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ORIGINAL PAPER

Synthesis, Properties and Crystal Structure of the 2,4-Dichlorophenyl-cyanoxime: A Powerful Carbonyl Reductase Inhibitor

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Abstract The compound 2,4-dichlorophenylcyanoxime (later H(2,4-diCl-PhCO)) has significance in its possible application in cancer chemotherapy treatments since it acts as an inhibitor of the human carbonic reductase. This enzyme decreases the effectiveness of anthracycline drug treatment of some types of cancer. The compound was synthesized in high yield at ambient conditions from 2,4-dichlorophenylacetonitrile, using gaseous methylnitrite. The compound was characterized by means of UV–visible, IR, ^{1}H, ^{13}C NMR spectroscopy and X-ray analysis. The cyanoxime crystallizes in a monoclinic space group $P2_1/c$ (#14) with unit cell constants: a = 3.7587(9) Å, b = 30.087(7) Å, c = 7.6874(17) Å, β = 96.163(3)°; V = 864.3(3) Å^3, Z = 4. The structure was solved, using direct methods, to final R indices [$I > 2\sigma$ (I)] R1 = 0.0551 (wR2 = 0.1217). The compound adopts a non-planar, *trans*-anti configuration with the value of the dihedral angle between the cyanoxime and dichlorophenyl planes equal to 50.61°.

Keywords Arylcyanoximes · Uncompetitive carbonyl reductase inhibitor · Crystal structure · UV–visible · IR · NMR spectroscopy

Introduction

Resistance to established chemotherapy treatments makes the search for effective compliments and alternatives necessary. Specifically, anthracycline drug treatments are noted to suffer from eventual resistance [1–3]. The human carbonyl reductase is believed to be responsible for the resistance to anthracycline drugs in cancer chemotherapy [4]. Certain cyanoximes have shown a propensity to be an inhibitor of the human carbonyl reductase [5]. Cyanoximes, in this regard, could serve as a complement to anthracycline treatments. The cyanoximes have the twofold benefit of lowering the resistance to chemotherapy treatments and also lowering the cardiotoxicity of the anthracycline drugs [5]. Current drugs, such as doxorubicin, can lead to eventual heart failure from prolonged treatment [6–8]. Of the cyanoximes previously studied, (Scheme 1), the 2,4-dichlorophenyl-cyanoxime (further as H(2,4-diClPhCO)) was found to be the most effective inhibitor, showing activity in the range around 10 μM. Thus, it was chosen for further analysis. The Pt and Pd complexes containing 2,4-diClPhCO$^-$ anions have previously been examined for their in vitro cytotoxicity against cancer cells [9], which was found to be at ~15 % of that for the anticancer drug cisplatin, which was used as a positive control. This paper describes the synthesis and further characterization of a biologically active 2,4-dichlorophenyl-cyanoxime.

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Experimental

General Considerations

All solvents and starting compounds, such as the 2,4-dichlorophenyl-acetonitrile, $NaNO_2$, and K_2CO_3 were of reagent grade, obtained from Aldrich and used without further purification. The identification of the target cyanoxime—H(2,4-diCl-PhCO)—was carried out using TLC on silica gel Al-backed plates from Merck, using the EtOAc:hexanes = 1:4 mobile phase. The melting point (without correction) of the cyanoxime was determined using the Mel-Temp digital apparatus in an open Pyrex glass capillary. An elemental analysis on the C, H, Cl content was done by the combustion method at the Atlantic Microlab Inc. (Norcross, GA).

Synthesis

Thinly sliced sodium (0.615 g) was placed into a flask containing 100 mL of *n*-propyl alcohol. Nitrogen gas was bubbled through the solution while it was stirred. It took about 30 min for the sodium to completely dissolve. The base solution is required to deprotonate the acidic hydrogen in the methylene group of the 2,4-dichlorophenylacetonitrile in the next step. Then 4.998 g (23.2 mM) of 2,4-dichlorophenylacetonitrile was dissolved in 25 mL of *n*-propanol with the help of a sonicator (Branson 1500 Ultrasound Bath) and a heat gun. The dissolved 2,4-dichlorophenylacetonitrile was added to the flask containing the C_3H_7ONa base prepared above; and gaseous methylnitrite CH_3ONO [5, 10] was bubbled through the reaction mixture, and within ~10 min it changed to a canary yellow color. The reaction mixture was placed in a refrigerator (overnight). The solvent was removed at first using the rotovap at +40 °C, and then under vacuum using an oil pump. The resulting thick yellow solid was re-dissolved in water and HCl:H_2O (1:4) was added dropwise to the solution until the pH was at a value of ~3. A pearl-white fine fibrous compound precipitated out of the clear solution. The compound was filtered, washed with water and dried in a dessicator. A representation of the synthesis can be seen in Scheme 2. The preparation was repeated three times and resulted in an average yield of 88 %; m.p. = 151 °C. The R_f value for the cyanoxime was found to be 0.26, while starting 2,4-dichlorophenylacetonitrile had a $R_f = 0.49$. A significant difference in the compounds' mobility allowed the reaction progress to be reliably monitored by co-spotting the probe from the reaction mixture and starting compound. The analysis for $C_8H_4Cl_2N_2O$ calculated (found, %): C—44.68 (44.89), H—1.87 (1.80), Cl—32.97 (31.59). ^{1}H NMR spectrum in dmso-d_6 (ppm): 14.24—OH oxime, 7.67 (6-position, doublet; $^3J = 8.4$ Hz), 7.60 (5-position, doublet of doublets; $^4J = 2.4$ Hz, $^3J = 8.4$ Hz); 7.85 (3-position, doublet; $^4J = 2.4$ Hz). $^{13}C\{^1H\}$ NMR spectrum in dmso-d_6 (ppm): 110.14 (CN-group), 127.73 (oxime), 128.56 (*ipso* carbon), 128.67 (6-carbon), 130.38 (5-carbon), 132.96 (3 carbon), 133.24 (4-carbon, to Cl), 136.74 (2-carbon, to Cl).

Solutions Studies

pK and pD Determination

Measurements of pK_a values for the synthesized 2,4-dichlorophenyl-cyanoxime were carried out using a Sirius Analytical Instruments automated titration station (Sussex, UK) equipped with a temperature-controlled bath. Since protonated cyanoximes HL are poorly soluble in water, all measurements were conducted in mixed solvent systems using dmso as a solubilizing co-solvent. Atenolol™ and Lidocaine™ (from Aldrich) were used for calibration of the instrument. Measurements consisted of the three-step multi-stage titration in water/dmso mixtures from 20 to 30 wt% with ionic strength adjusted to 0.15 with KCl. The values were extrapolated to "zero" DMSO content to obtain an aqueous pK_a value using the Yasuda–Shedlovsky procedure. The pH in titration experiments ranged from 3 to 11. Potentiometric titration experiments were also carried out for measurements of log P and log D (where P is the partition coefficient between water and *n*-octanol, and D is a diffusion coefficient).

Spectroscopy

UV–Vis data were collected for both the protonated and deprotonated species of H(2,4-diClPhCO). The compound was deprotonated with KOH dissolved in alcohol. The absorbance was measured (EtOH, 0.1 cm cuvette) at room temperature in the range of 200–1,100 nm using an HP 8453 diode array spectrophotometer. The ^{1}H and $^{13}C\{^1H\}$ NMR spectra were collected on a Varian INova spectrometer at 399.85 and 100.54 MHz frequencies respectively. Samples were dissolved in dmso-d_6, and the measurements were made at room temperature. The IR spectra of the initial compound 2,4-dichlorophenylacetonitrile and the cyanoxime were recorded on a Bruker ALPHA-P in ATR mode.

X-ray Crystallography

Crystal Growth

The crystallization process required a small amount (0.1–0.3 g) of the cyanoxime to be dissolved in a solvent (ethanol, diethyl ether, and acetonitrile). The dissolved compound was then added to a long narrow test tube. On

Table 1 Crystal data and structure refinement for H(2,4-diCl-PhCO)

Empirical formula	$C_8H_4Cl_2N_2O$
Formula weight	215.03
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c, #14
Unit cell dimensions	a = 3.7587(9) Å, α = 90°
	b = 30.087(7) Å, β = 96.163(3)°
	c = 7.6874(17) Å, γ = 90°
Volume	864.3(3) $Å^3$
Z	4
Density (calculated)	1.652 Mg/m^3
Absorption coefficient	0.704 mm^{-1}
F(000)	432
Crystal size	0.30 mm × 0.21 mm × 0.20 mm
Theta range for data collection	1.35–28.28°
Index ranges	$-4 \leq h \leq 5$, $-40 \leq k \leq 40$, $-10 \leq l \leq 10$
Reflections collected	10,273
Independent reflections	2,110 [R(int) = 0.0834]
Completeness to theta = 28.28°	99.4 %
Absorption correction	Numerical from crystal faces indexing
Max. and min. transmission	0.8719 and 0.8175
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2,110/0/134
Goodness-of-fit on F^2	1.093
Final R indices [I > 2σ (I)]	R1 = 0.0551, wR2 = 0.1217
R indices (all data)	R1 = 0.0663, wR2 = 0.1270
Largest diff. peak and hole	0.407 and −0.385 e $Å^{-3}$

top of this solution, hexane was slowly added. The test tubes were left to cool in a refrigerator. After several days, as the hexane slowly dispersed into the solution below, crystals of the target compound appeared on the wall of the tube.

Data Collection

A clear, colourless, block-like specimen of $C_8H_4Cl_2N_2O$, whose approximate dimensions were 0.20 mm × 0.21 mm × 0.30 mm, was used for the X-ray crystallographic analysis (SI 1). Measurements were carried out at 120 K using Bruker APEX 2 diffractometers equipped with a SMART CCD area detector. The intensity data were collected in ω-scan mode using the Mo tube (Kα radiation; λ = 0.71073 Å) with a highly oriented graphite monochromator. Intensities were integrated from four series of 364 exposures, each covering 0.5° in ω, and the total data set being a sphere [11]. The space group determination was done with the aid of XPREP software [12, 13]. Numerical absorption corrections were applied based on crystal face indexing obtained using actual images recorded by the video-microscope camera (SI 2). The following data processing was performed using the SADABS program that was included in the Bruker AXS software package [14]. The structures were solved by direct methods and refined by least squares on weighted F^2 values for all reflections using the SHELXTL program [12, 13]. All atoms received assigned anisotropic displacement parameters and were refined without positional constraints. Hydrogen atoms in the structure were all objectively found on a difference map and refined. Crystal data for the studied compound are presented in Table 1, while bond lengths and valence angles are summarized in Table 2. Figures for the crystal structures of these complexes were drawn using Mercury 4.1.2 and ORTEP 32 software [15, 16] at a 50 % thermal ellipsoids probability level. The PLATON checks of crystallographic data and actual CIF file for reported structure can be found in the Supplementary Information section. The structure was deposited onto CSDC.

Results and Discussion

Acidity and Media Distribution Studies

The H(2,4-diCl-PhCO) represents a weak acid with $pK_a = 6.44 \pm 0.02$. The protonated compound itself is not soluble in water, but, at a pH above 7.5, it dissolves completely in aqueous solutions with the formation of a yellow anion. Since this cyanoxime showed the best inhibitory activity against the human carbonyl reductase enzyme, it was important to investigate its distribution between aqueous and non-aqueous solutions. This compound can be further developed as a medical drug administered during the course of anticancer treatment involving *anthracycline-family* antibiotics. Therefore, an

Table 2 Selected bond lengths (Å) and valence angles (°) for H(2,4-diCl-PhCO)

Bonds	Angles
C(1)–N(1) = 1.291(3)	N(1)–C(1)–C(2) = 121.5(3)
C(1)–C(2) = 1.449(4)	N(1)–C(1)–C(3) = 117.6(2)
C(1)–C(3) = 1.479(4)	C(2)–C(1)–C(3) = 120.7(2)
C(2)–N(2) = 1.140(4)	N(2)–C(2)–C(1) = 177.3(3)
C(4)–Cl(1) = 1.733(3)	C(4)–C(3)–C(8) = 118.2(2)
C(6)–Cl(2) = 1.739(3)	C(5)–C(4)–Cl(1) = 117.9(2)
N(1)–O(1) = 1.377(3)	C(3)–C(4)–Cl(1) = 120.6(2)
O(1)–H(1O) = 0.84(4)	C(7)–C(6)–Cl(2) = 119.4(2)
	C(5)–C(6)–Cl(2) = 118.6(2)
	C(1)–N(1)–O(1) = 112.0(2)
	N(1)–O(1)–H(1O) = 101(2)

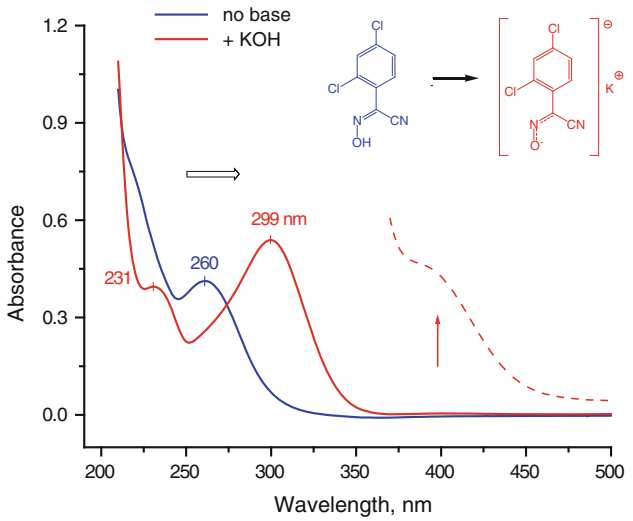


Fig. 1 UV–visible spectra of protonated (*blue*) deprotonated (*red*) with KOH cyanoxime in ethanol showing bathochromic shift of $\pi \rightarrow \pi^*$ bands. The K^+ salt was obtained in situ and was not isolated. An inset shows ×100 magnified region of low-intensity $n \rightarrow \pi^*$ transition in visible region, which is shown in detail in Fig. 2 (Color figure online)

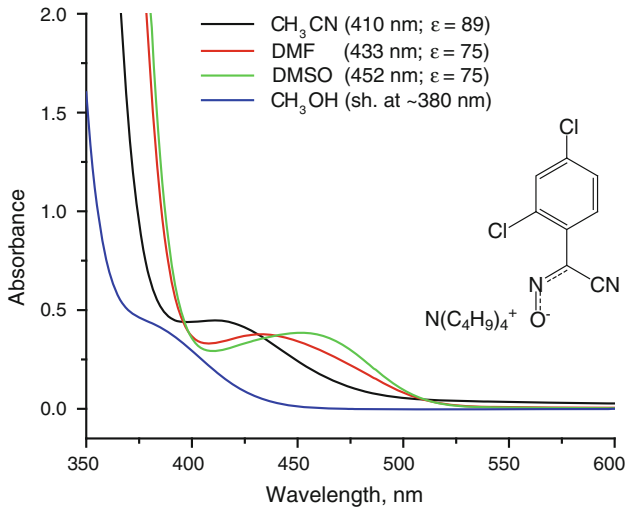


Fig. 2 Spectra of the 2,4-dichlorophenylcyanoxime anion (as tetrabutylammonium salt) in several solvents in visible region in the area of $n \rightarrow \pi^*$ transitions (Color figure online)

investigation of its partitioning between hydrophobic and hydrophilic media was warranted. A dual-phase titration of the cyanoxime at +25 °C over a pH range, during which it passes from fully protonated to fully deprotonated forms, was performed. Some specific details of the procedure are shown in SI 3–5. The compound has a high log P value of 3.65, which testifies that this cyanoxime is highly permeable. This fact can explain the high inhibitory activity of the H(2,4-diCl-PhCO) for the carbonyl reductase enzyme. Another inhibitor of this enzyme is menadione—2-methyl-1,4-naphthoquinone—also a highly lipophilic compound. That explains the similar nature of the enzyme's active site, but does not explain why the structurally different molecules have a similar inhibitory effect on the enzyme. The lipophilicity profile (log D vs pH) shows a drop in the distribution coefficient at a pH above 5.5 when the deprotonation of the compound begins to occur (SI 5).

Spectroscopic Properties

The title compound easily undergoes deprotonation at basic conditions in aqueous and non-aqueous solvents with the formation of the mono-anion L^-. There is a delocalization of negative charge throughout the anion at which the *nitroso*- form is dominant (SI 6). Besides, the 2,4-dichlorophenyl cyanoxime anion, L^-, demonstrates a redistribution of intensities and a considerable bathochromic shift of $\pi \rightarrow \pi^*$ bands in the UV-spectrum (Fig. 1), as compared to its protonated precursor HL (SI 7). The protonated cyanoxime HL is colorless, but it gains a canary yellow color in basic solutions due to the presence of a weak band of $n \rightarrow \pi^*$ transition ($\varepsilon = 75$–90, depending on solvent) in the *nitroso* chromophore in the visible region of the spectrum (Fig. 2). The cyanoxime anion demonstrates a pronounced negative solvatochromism [17–19]. Thus, the position of the $n \rightarrow \pi^*$ band in visible spectra changes in an unexpected way with the change of the solvent used for studies (Fig. 2). That is reflected in the bathochromic shift of this band in less-polar solvents [17]. Since the K^+ salt of the cyanoxime is not soluble in most organic solvents, tetrabutylammonium hydroxide was used for the cyanoxime deprotonation in a solvent of interest. Thus, the formed cyanoxime salt of tetraalkylammonium is soluble in all studied solvents. Its observed behavior is in line with the similar performance established for the NO_2^- anion [18] and other cyanoximes [20, 21]. A linear correlation

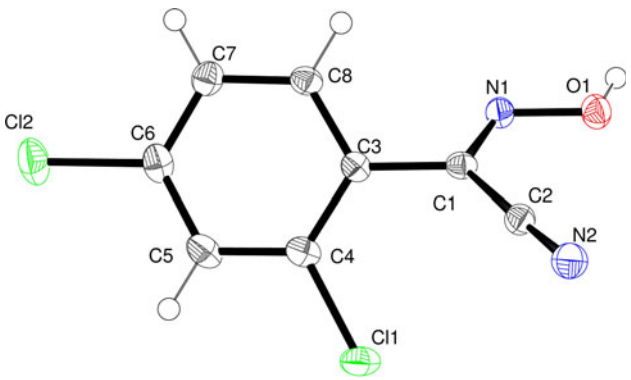


Fig. 3 Molecular structure and numbering scheme for the H(2,4-diCl-PhCO); an ORTEP drawing at 50 % thermal ellipsoids probability level

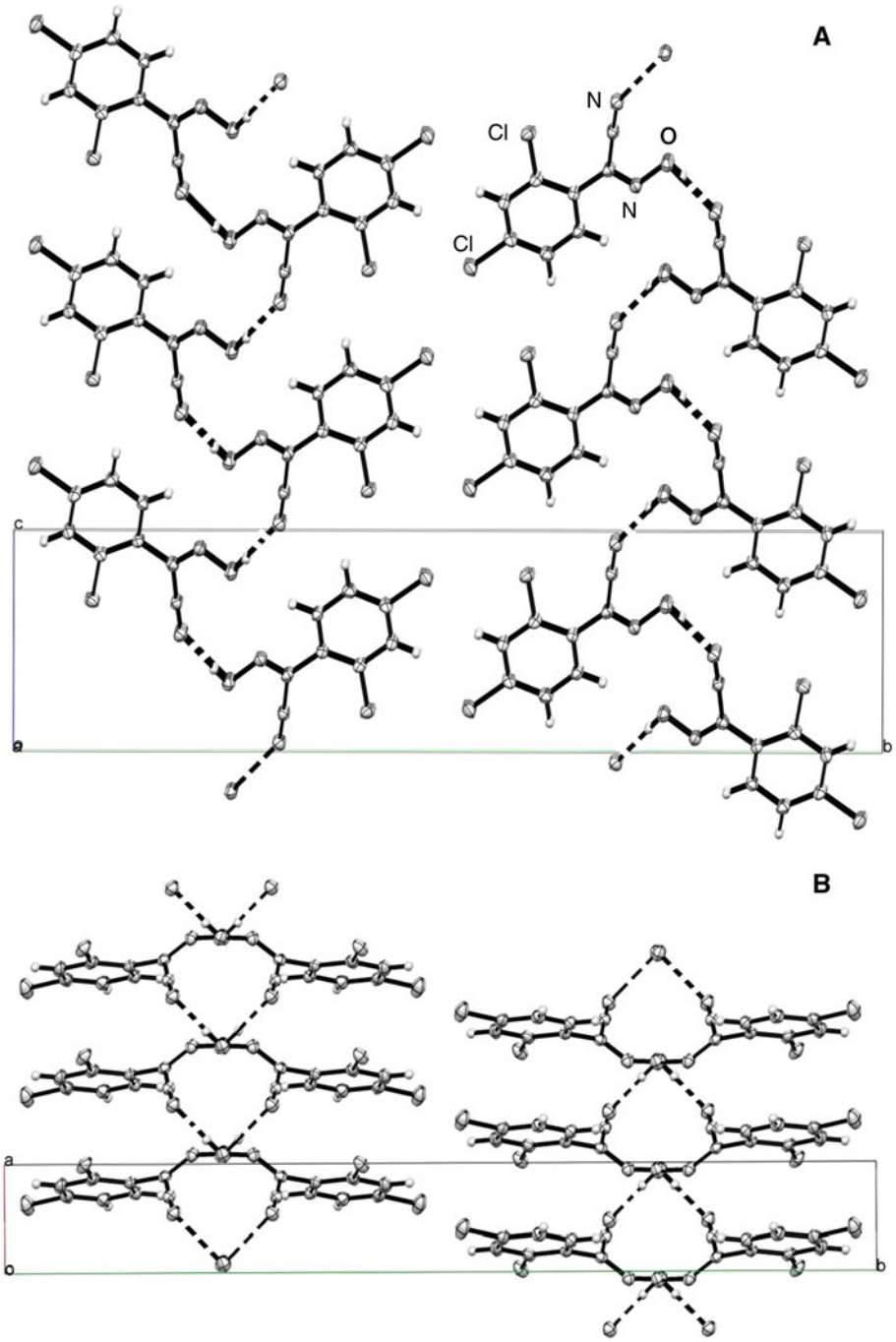


Fig. 4 Two orthogonal views of the structure of H(2,4-diCl-PhCO) showing H-bonding [(**a**), view along *a*] and π-stacking [(**b**), view along *c*] between H-bonded sheets

was found between the energy of the $n \rightarrow \pi^*$ transition in the nitroso chromophore in visible spectrum and Kosover's solvation energy Z [22, 23], pK_a of the alcohol ROH used (SI 8).

The ^1H NMR spectrum of the freshly prepared solution of the cyanoxime in the same solvent showed a rather narrow singlet of the oxime group at ~14.3 ppm which evidenced the absence of dynamic processes in the solution and the presence of only one isomer (SI 9, 10). This is confirmed in the $^{13}C\{^1H\}$ NMR spectra of the compound HL which showed one set of signals that correspond to only one geometrical isomer (presumably *anti*) present in DMSO solutions. Observed findings are different from the more common mixture of *syn*- and *anti*- isomers typically present in solutions of other aryl-cyanoximes [9, 24].

Crystal Structure

A search of the CCDC database on the presence of a 2,4-dichlorophenyl fragment resulted in 809 hits that also includes other 3-,5-, 6-differently-substituted 2,4-dichlorophenyl groups. Out of that large number, 387 structures

Table 3 Hydrogen bonds for H(2,4-diCl-PhCO) (Å and °)

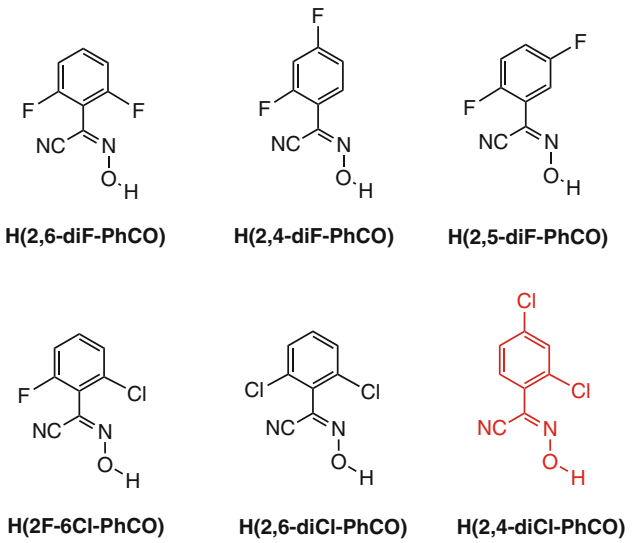
D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
O(1)–H(1)···N(2) #1	0.84(4)	2.02(4)	2.838(3)	165.2(2)

Symmetry transformations used to generate equivalent atoms
#1 x + 1, −y + 1/2, z + 1/2

contained a pure, non-derivatized 2,4-dichlorophenyl fragment. Our title compound was not present in the database, and the most closely structurally related findings are: 2,4-dichlorophenylaldoxime (ref code ADELUR, [25]), 2,4-dichlorobenzo hydroxamic acid (ref code FONHUM, [26]), and (Z)-1-(2,4-Dichlorophenyl)ethan-1-one semicarbazone (ref code HUCRED, [27]).

For the title compound, a total of 1,456 frames representing a full sphere of data were collected, and the integration of the data using a monoclinic unit cell yielded a total of 10,273 reflections to a maximum θ angle of 28.28° (0.75 Å resolution). 2,110 reflections were independent and the average redundancy was 4.869 with completeness to 2Θ angle equal 99.4 % (R(int) = 8.34 %, R(σ) = 6.32 %) and 1,820 reflections (86.26 %) had greater than $2\sigma(F^2)$ intensities. The structure of H(2,4-diCl-PhCO) was solved using direct methods and refined using the Bruker SHELXTL Software Package [14], using the monoclinic space group $P2_1/c$ (#14) with Z = 4 for the formula unit $C_8H_4Cl_2N_2O$. The final anisotropic full-matrix least-squares refinement on F^2 with 119 variables converged at R1 = 5.55 (Table 1). All hydrogen atoms in the structure were found on the electron difference map and refined objectively.

The molecular structure and numbering scheme for H(2,4-diCl-PhCO) is shown in Fig. 3, while the organization of the structure and packing diagrams are presented in Fig. 4 (SI 11). The values of selected bond lengths and valence angles are shown in Table 2. The cyanoxime adopts a non-planar *trans*-anti configuration in solid state. The dihedral angle between mean planes of the phenyl ring and the plane of cyanoxime-group O1–N1–C1–C2–N2 is 50.61°. For comparison it is interesting to note that a similar compound—2,4-dichlorophenylaldoxime [25]—is almost planar and the dihedral angle between the aromatic ring and aldoxime fragment is 17.57°. Bonds in the cyanoxime group in the structure of H(2,4-diCl-PhCO) are in the range typically observed for this class of compounds: N(1)–O(1) = 1.377(3) and C(1)–N(1) = 1.291(3) Å (Table 2). Geometrical parameters for the dichlorophenyl fragment are normal for this group. Individual molecules of the cyanoxime form an elegant system of H-bonds between the nitrogen atom N2 of the cyano-group and the oxime OH-group of the neighboring molecule when packed into the crystal (Fig. 4; Table 3). H-bonded molecules of the



Scheme 1 Disubstituted arylcyanoximes with cytotoxic properties

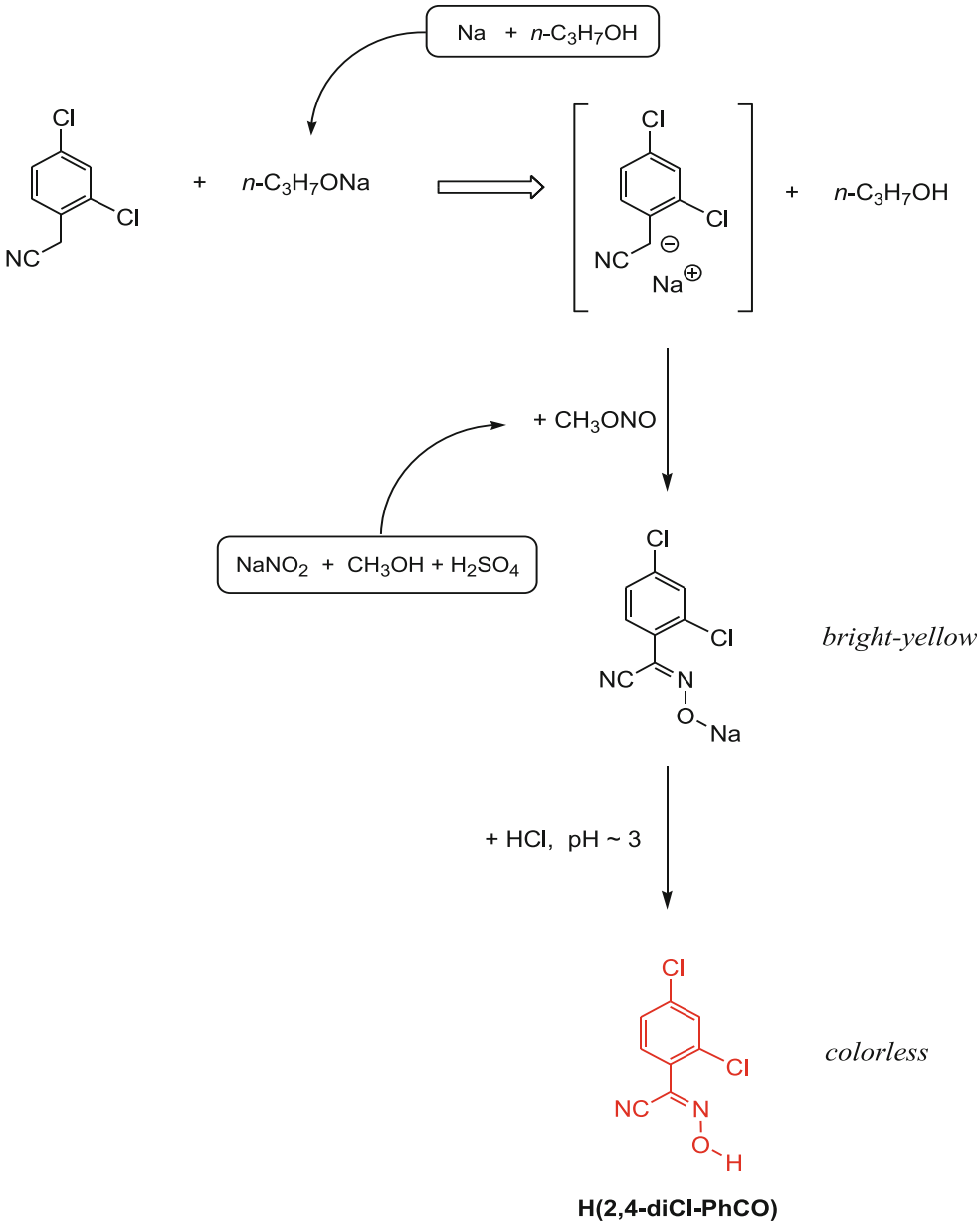
compound are arranged into sheets that form the ladder-type structure, due to a significant dihedral angle (50.61°) between the aromatic and cyanoxime groups. Slipped π–π stacking interactions between chloro-phenyl groups at a distance of 3.695 Å contribute to the lattice formation and its overall architecture. The "slip angle" between two π–π interacting phenyl groups is 21.20°. The distance between the two closest centroids of the chlorophenyl-rings is 3.759 Å. The crystal packing of the H(2,4-diCl-PhCO) can be described as a staircase (or ladder-type) of H-bonded 2D-sheets of molecules that are joined into columns by means of π–π stacking interactions to form an elegant 3D network. Columns are held together via van-der-Waals forces between dichlorophenyl-groups, with a sheer plane of the crystal passing through the middle of the *b*-direction (Fig. 4; SI 11).

The crystal structure of the cyanoxime contributes to the area of structurally characterized chlorinated aromatic compounds, which possess a variety of properties valuable for biomedical research. The next steps in this work are: (1) to synthesize and test on enzymatic inhibitory activity several other small molecules containing the 2,4-dichlorophenyl fragment known structures of which are deposited into the CCDC database, and (2) to provide a structure–activity relationship analysis for a series of studied chlorinated compounds in order to select the best performing molecule with optimized properties.

Conclusions

A high-yield preparation of an important non-competitive inhibitor of the carbonyl reductase enzyme—2,4-dichlorophenylcyanoxime—has been described in detail. The

Scheme 2 Synthetic route for target compound H(2,4-diCl-PhCO)



compound was characterized by means of solutions studies that include pK_a, partitioning and pD coefficients measurements, ^{1}H, ^{13}C NMR, IR and UV–visible spectroscopy and the X-ray analysis. It was found that the cyanoxime represents a weak organic acid that possesses high permeability into non-polar lipophilic media. The crystal structure revealed that the cyanoxime adopts a non-planar *trans*-anti configuration in solid state. The compound is packed into a crystal by means of the H-bonding between the molecules that formed 2D-sheets arranged in a staircase fashion, which then assemble into the 3D framework via slipped π–π stacking interactions between aromatic systems.

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