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ORIGINAL PAPER

Structural Conformation of a Novel Piperidine-4-One Derivative: 1-Acryloyl-3-Methyl-2,6-Dip-Tolylpiperidine-4-One

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Abstract The novel 3-methyl-2,6-dip-toylpiperidine-4-one was acylated by 3-chloropropanoychloride and subjected for dehydrohalogenation. The synthesized compound was characterized by spectroscopic techniques and finally confirmed by X-ray diffraction studies. The molecule crystallizes in the monoclinic crystal class in the space group C_2/c with cell parameters $a = 18.538(2)$ Å, $b = 9.9050(1)$ Å, $c = 22.954(2)$ Å, $\beta = 94.486(8)°$ and $Z = 8$. The piperidine ring adopts a twist boat conformation.

Keywords Alkaloid · Piperidine-4-one · Chloropropanoylchloride · Twist boat conformation

Introduction

The nitrogen heterocyclics particularly piperidines are an important group of compounds in the field of medicinal chemistry owing to the fact that these can frequently be recognized in the structure of numerous naturally occurring alkaloid and synthetic compounds with interesting biological and pharmacological properties, which has been reviewed by Prostakov and Gaivoronskaya [1]. Piperidones are also reported to possess analgesic, [2, 3] anti-inflammatory, [3] stimulant and depressant activity on central nervous system (CNS), [4–8] local anaesthetic, [4, 9] anticancer [10] and antimicrobial activity [11]. The earlier reports indicated that the significant biological activities of piperidones were associated with aromatic substituents at C2 and/or C6 positions [6, 11]. 5-Alkyl/aryl substituted-1,2,3-trimethylpiperidine-4-one were reported to influence arterial pressure, respiration and nerve activity [12]. A series of *N*-methyl-(*E*)-3,5-bis(arylidine)-4-piperidones carrying a variety of aryl and heteroaryl groups were reported to have a combination of antiviral and antitumor activities [13]. N aceylation of substituted piperidine-4-one with chloropropanoyl chloride produced biologically active moieties.

Experimental Section

Melting point of the molecule was determined using Thomas Hoover apparatus at the heating rate of 1 °C per minute and was uncorrected. Carbon, nitrogen and hydrogen contents of the molecule were determined by micro analytical techniques on Elementar Vario EL III CHNS (carbon, hydrogen, nitrogen, sulphur) analyzer. Infrared spectra was recorded on Jasco FT-IR 4100 spectrophotometer with potassium bromide pellets in the region 3,500–500 cm^{-1} and only significant absorption levels are listed. The H^1 NMR spectra of the molecules were recorded using TMS (tetramethylsilane) as a reference standard in DMSO-d6 (dimethyl sulfoxide duterated) solvent on Bruker AMX 300 MHz High Resolution Multinuclear FT-NMR Spectrometer and mass spectra on a Waters-Q-TOF Ultima spectrophotometer.

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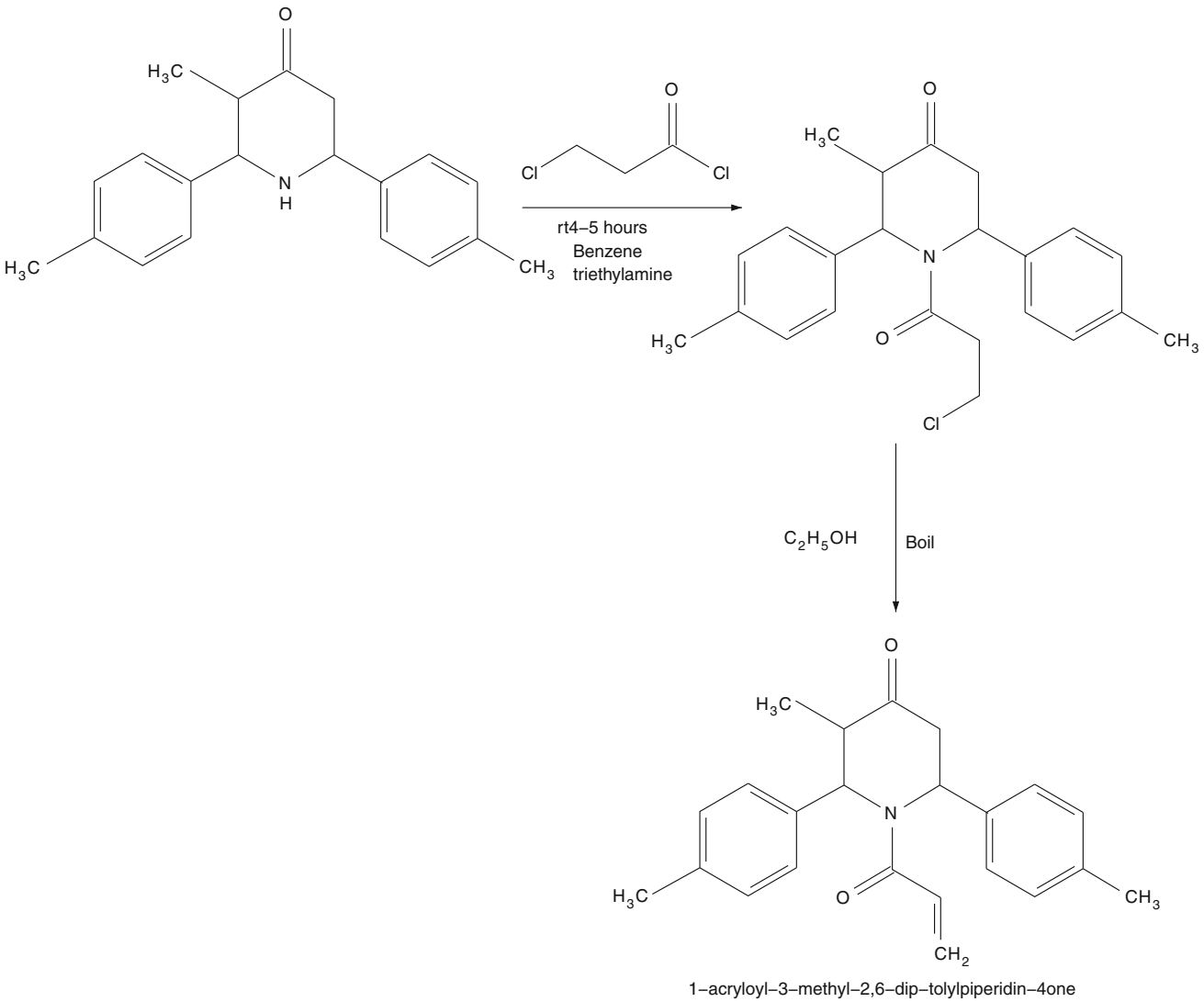
Spectral Data of 1-Acryloyl-3-Methyl-2,6-Dip-Tolylpiperidine-4-One

Analytical data; experimental (calculated) C = 79.69 (79.51), H = 7.46(7.25), N = 4.14(4.03); Melting point: 124 °C; Yield:92.3%; MS(*m*/*z*):347; IR (KBr, cm^{-1}):3096, 3028, 2974, 2940, 2877, 2824 (C–H stretching), 1720(C=) stretching), 1645 (N–C=O stretching), 1609, 1513, 1451, 1371, 1327, 1266, 1183, 1119, 1050, 977, 825, 798, 548. ^{1}H NMR (δ, ppm): 3.1 (d, CH, 1H, C_{5a}); 2.85 (dd, CH, 1H, C_{5b}); 3.05 (t, CH, 1H, C_3); 6.3 and 5.6 (d, CH_2, 2H, $CH{=}CH_2$); 6.5 (t, CH, H, CH–C=o); 5.26 (s, CH, 1H, C_2); 5.75 (s,CH, 1H, C_6); 7.13–7.33 (m Ar–H, 8H, aromatic protons); 1.06 (d, CH_3, 3H, CH_3, at C_3); 2.35 (s, CH_3, 6H, $2CH_3$ in two benzene ring).

Synthesis and Crystallization

3-Methyl-2,6-dip-tolypiperidine-4-one was synthesized according to literature method [14] by the condensation of 2-butanone, p-tolaldehyde and ammonium acetate in 1:2:1 ratio. Further it was acylated as follows. To a well stirred solution of 3-methyl-2,6-dip-tolylpiperidin-4-one (5 mmol) in benzene (30 mL) and triethylamine (15 mmol), 3-chloropropanoyl chloride in benzene (20 mL) was added slowly for about an hour. Then the reaction mixture was stirred at room temperature for about 4–5 h. After completion of the reaction, it was poured into cold water (500 mL) and extracted in ethyl acetate twice in 50 mL portions. The ethyl acetate layer was washed with 5% sodium bicarbonate solution followed by distilled water. Further, it was dried in



Scheme 1 Synthesis of 1-acryloyl-3-methyl-2,6-dip-tolylpiperidine-4-one

Table 1 Experimental crystallographic data

Empirical formula	$C_{24}H_{27}NO_3$
Formula weight	377.47
Temperature	293(2)K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C_2/c
Cell dimensions	$a = 18.538(2)$ Å
	$b = 9.9050(1)$ Å
	$c = 22.954(2)$ Å
	$\beta = 94.486(8)°$
Volume	4201.9(8) Å^3
Z	8
Density (calculated)	1.193 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F_{000}	1616
Crystal size	0.30 × 0.27 × 0.25 mm
Theta range for data collection	2.88°to 25.03°
Index ranges	$-21 \leq h \leq 22$
	$-11 \leq k \leq 11$
	$-25 \leq l \leq 25$
Reflections collected	6442
Independent reflections	3536 [$R_{(int)} = 0.0343$]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3536/0/257
Goodness-of-fit on F^2	1.042
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0727$, $wR_2 = 0.2107$
R indices (all data)	$R_1 = 0.0995$, $wR_2 = 0.2429$
Largest diff. peak and hole	0.293 and −0.387 e. Å^{-3}
CCDC deposit number	CCDC 747592

anhydrous sodium sulphate and distilled under reduced pressure to get crude 1-(3-chloropropanoyl)-3-methyl-2,6-dip-tolylpiperidine-4-one. This semisolid was dissolved in excess of distilled ethanol and heated to boil. The title compound was crystallized by slow evaporation in ethanol. The crystals were filtered washed with distilled ethanol and desiccated (Scheme 1). The constitution of 1-acryloyl-3-methyl-2,6-dip-tolylpiperidine-4-one was supported by IR, ^{1}H & ^{13}C NMR and Mass spectral studies.

Crystal Structure Determination

A single crystal of suitable size was chosen for X-ray diffraction studies. The data were collected at room temperature on a DIPLabo Image Plate system with graphite monochromated radiation MoK_α. Each exposure of the image plate was set to a period of 400s. Thirty-six frames of data were collected in the oscillation mode with an oscillation range of 5° and processed using Denzo [15]. The reflection were merged with Scalepack. All the frames could be indexed using a primitive monoclinic lattice. The structure was solved by direct methods using SHELXS-97 [16]. Least-squares refinement using SHELXL-97 [16] with isotropic displacement parameters for all the non-hydrogen atoms converged the residual to $R_1 = 0.1790$. Subsequent refinements were carried out with anisotropic

Table 2 Bond lengths (Å) and bond angles (°)

Atoms	Length	Atoms	Length
O10–C9	1.223(3)	C20–C2	1.520(4)
N1–C9	1.363(3)	C25–C24	1.384(5)
N1–C6	1.486(3)	C18–C17	1.392(5)
N1–C2	1.486(3)	C2–C3	1.526(4)
O7–C4	1.206(3)	C21–C22	1.371(5)
C13–C18	1.376(4)	C11–C12	1.308(4)
C13–C14	1.387(4)	C24–C23	1.387(5)
C13–C6	1.518(4)	C17–C16	1.384(6)
C9–C11	1.486(4)	C22–C23	1.381(5)
C5–C4	1.500(5)	C23–C26	1.514(5)
C5–C8	1.527(4)	C14–C15	1.365(5)
C5–C6	1.552(4)	C15–C16	1.369(5)
C4–C3	1.507(5)	C16–C19	1.518(6)
C20–C21	1.387(4)	O30–C31	1.318(7)
C20–C25	1.391(4)	O30–O30	1.499(1)
C9–N1–C6	123.6(2)	C24–C25–C20	121.0(3)
C9–N1–C2	116.3(2)	C13–C18–C17	120.6(4)
C6–N1–C2	119.4(2)	N1–C2–C20	112.5(2)
C18–C13–C14	117.7(3)	N1–C2–C3	108.4(2)
C18–C13–C6	120.9(3)	C20–C2–C3	116.3(2)
C14–C13–C6	121.3(3)	C22–C21–C20	121.5(3)
O10–C9–N1	120.8(3)	C4–C3–C2	112.4(3)
O10–C9–C11	120.3(3)	C12–C11–C9	121.3(3)
N1–C9–C11	118.8(3)	C25–C24–C23	121.5(3)
C4–C5–C8	112.1(3)	C16–C17–C18	121.1(3)
C4–C5–C6	112.4(2)	C21–C22–C23	121.9(3)
C8–C5–C6	111.4(3)	C22–C23–C24	117.0(3)
N1–C6–C13	112.3(2)	C22–C23–C26	122.1(3)
N1–C6–C5	110.5(2)	C24–C23–C26	120.9(3)
C13–C6–C5	109.9(2)	C15–C14–C13	121.1(3)
O7–C4–C5	122.9(3)	C14–C15–C16	122.1(4)
O7–C4–C3	121.4(3)	C15–C16–C17	117.3(3)
C5–C4–C3	115.7(2)	C15–C16–C19	121.5(4)
C21–C20–C25	117.0(3)	C17–C16–C19	121.2(4)
C21–C20–C2	123.5(3)	C31–O30–O30	115.2(7)
C25–C20–C2	119.4(3)		

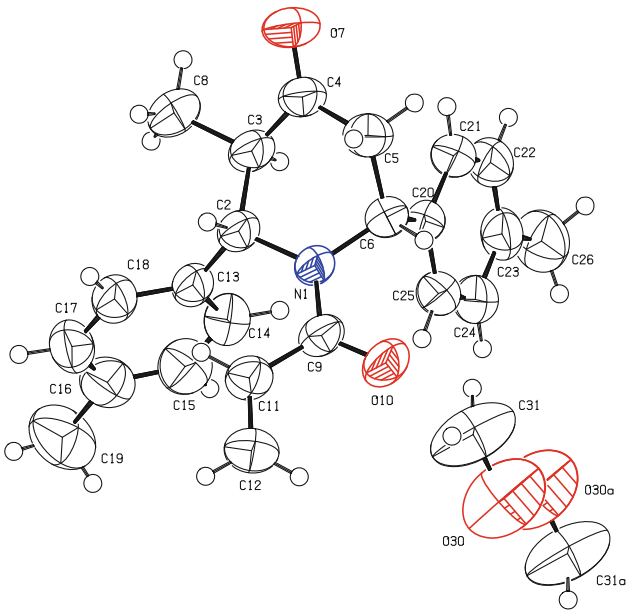


Fig. 1 ORTEP of the molecule with thermal ellipsoids drawn at 50% probability

thermal parameters for the non-hydrogen atoms. After eight cycles of refinement the residuals converged to 0.0727. The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on their parent atoms. The crystallographic data have been deposited in Cambridge Crystallographic Data Center, under reference CCDC 747592.

Results and Discussion

The details of crystal data and refinement are given in Table 1. The bond lengths and bond angles of all the non-hydrogen atoms (Table 2) are in good agreement with the standard values[17]. Figure 1 represents the ORTEP [18] diagram of the molecule with thermal ellipsoids drawn at 50% probability. In the title compound $C_{24}H_{27}NO_3$, the heterocyclic ring adopts a twist boat conformation with the atoms N1 and C6 deviating by 0.396(3) Å and −0.275(3) Å from the plane (Cremer and Pople, 1975) defined by the atoms N1/C2/C3/C4/C5/C6. The ring-puckering parameters [19] are given by $Q = 0.692(3)$ Å, $\theta = 92.5(2)°$ and $\phi = 256.0(3)°$, respectively. The substituent at C6 is in equatorial conformation as indicated by the dihedral angle of 85.62(2)° between piperidine and phenyl ring and the substituent at C2 has a dihedral angle of 68.36(2)° between the piperidine ring and phenyl ring. The piperidine ring in the molecule has a weighted average torsion angle of 37.47°. The torsion angle value of −177.7(3)° for N1–C2–C3–C8 indicates that methyl group substituted at C3 is oriented in *−anti-periplanar* conformation. The torsion angle value of 176.5(3)° for C2–N1–C9–O10 indicates that O10 is oriented in *+anti-periplanar* conformation. The acryloyl group substituted at N1 is oriented in *+anti-periplanar* conformation as indicated by the torsion angle value of 165.9(2)° for C6–N1–C9–C11. No classic hydrogen bonds are observed. The packing of the molecules down *a* axis is shown in the Fig. 2.

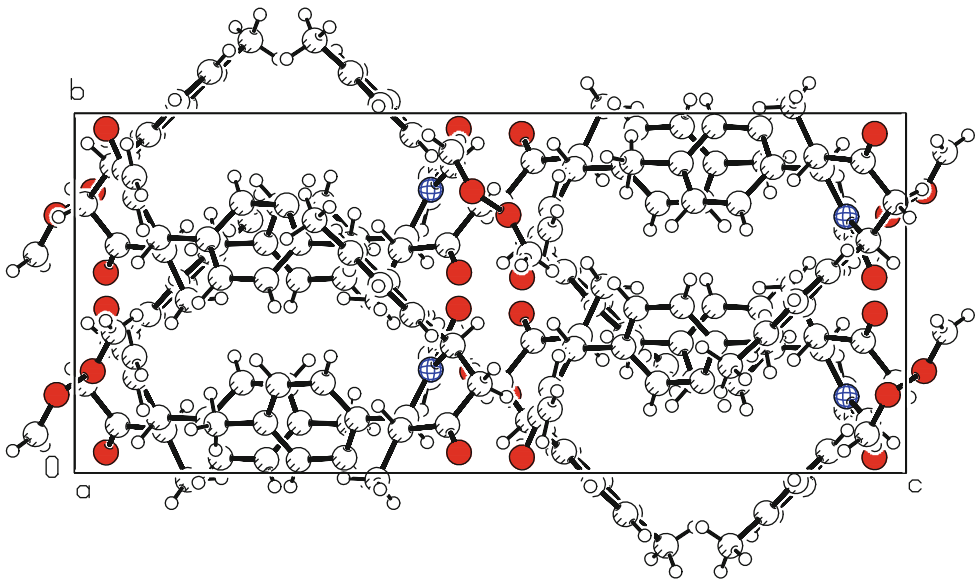


Fig. 2 Packing of the molecule when viewed along the *a* axis

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