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ORIGINAL PAPER

Rapid Eco-Friendly Synthesis and Structure of 3-Hydroxy-3-nitromethyl-1,3-dihydro-indol-2-one

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Abstract 3-Hydroxy-3-nitromethyl-1,3-dihydro-indol-2-one was synthesized from isatin by Henry reaction using an eco-friendly method and characterized by NMR and MS. The crystal structure was determined from single-crystal X-ray diffraction data. It crystallizes in the orthorhombic space group, Pbca, with unit cell dimensions $a = 10.515$ (2) Å, $b = 7.3736$ (14) Å, and $c = 23.261$ (4) Å. The two rings are coplanar and the angle between hydroxyl group and nitromethyl group is 109.07(9)°. In the crystal structure, intermolecular N–H···O and O–H···O hydrogen bonds are responsible for the formation of a 3-dimensional network. No intramolecular hydrogen bond exists.

Keywords 3-Hydroxy-3-nitromethyl-1,3-dihydro-indol-2-one · X-ray structure · Henry reaction

Introduction

In recent years, many 3-nitromethylene-1,3-dihydro-indol-2-one derivatives has been synthesized, due to the interesting bioactivities of isatin (indole-2,3-dione) derivatives [1–3]. 3-Hydroxy-3-nitromethyl-1,3-dihydro-indol-2-one(**1**), an important intermediate in the synthesis of 3-nitromethylene-1,3-dihydro-indol-2-one, has been synthesized by Henry reaction between isatin and nitromethane [1, 2]. Dehydration of **1** as well as its derivatives provides 3-nitromethylene-1,3-dihydro-indol-2-one, which is used as a dipolarophile in 1,3-dipolar cycloadditon reactions to synthesis spiro-oxindol compounds [2, 3]. The reported Henry reactions between isatin and nitromethane was catalyzed by a strong organic base catalyst, DBU(1,8-Diazabicyclo[5.4.0]undec-7-ene), giving moderate yield [1, 3]. Moreover, this costly catalyst suffers from decomposition in air or under light.

Diethylamine, a stable weak base with low price, has shown great catalysis activity in Aldol reaction between methyl ketone and isatin [4]. Since Henry reaction is an aldol-type reaction [5, 6], it is anticipated that great activity of diethylamine can be displayed in Henry reaction between isatin and nitromethane. In this article, we employed diethylamine as catalyst in the synthesis of the title compound (**1**) (shown in Scheme 1) and determined its crystal structure by single-crystal X-ray.

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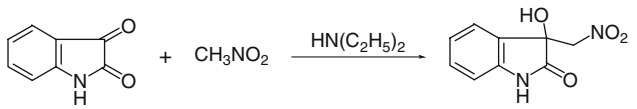
Experimental

All starting materials and solvents (A.R. grade) were commercially available and were used without further purification. NMR spectra was recorded in the stated solutions, on a Bruker Drx-400 spectrometer, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C; δ values are reported in ppm and J values in hertz. Mass spectra were recorded on a Micromass PlatformIIspectrometer, using the direct-inlet system operating in the electron impact (EI) mode at 75 eV.

Synthesis of 3-Hydroxy-3-nitromethyl-1,3-dihydro-indol-2-one

Isatin (0.294 g, 2 mmol) was dissolved in nitromethane (15 mL), and a drop of diethylamine was added in. The



Scheme 1 Synthesis of 3-hydroxy-3-nitromethyl-1,3-dihydro-indol-2-one

mixture was stirred under room temperature for a few minutes until the solution turned to be colorless from orange. The solvent was distilled off under reduced pressure to give the target product as a white powder. Colorless crystals of **1** were obtained in ethanol by recrystallization. ^{1}H-NMR (D_6-DMSO, 400 MHz), δ: 10.56 (1H, s), 7.39 (1H, d, $J = 7.2$ Hz), 7.26 (1H, td, $J = 7.6$, 1.2 Hz), 6.98 (1H, t, $J = 7.6$ Hz), 6.85 (1H, d, $J = 7.6$ Hz), 6.75 (1H, s), 4.99 (2H, dd, $J = 12.8$, 8.0 Hz); ^{13}C-NMR (D_6-DMSO, 100 MHz), δ: 176.0, 142.6, 130.3, 127.9, 124.7, 121.9, 110.1, 78.5, 72.8; MS (EI) *m/z*: 208 (M^+).

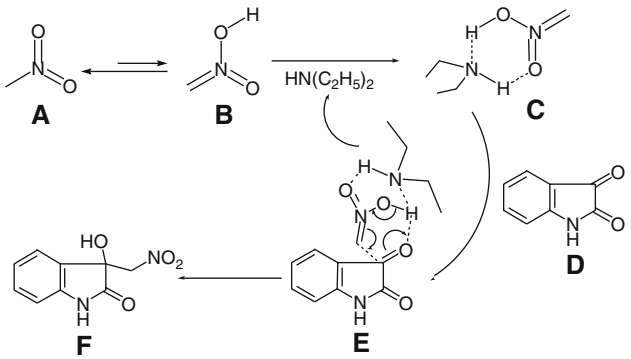
X-Ray Data Collection and Structure Refinement

All H atoms were positioned geometrically, with C–H = 0.93–0.98 Å, and refined with a riding model, with $U_{iso}(H) = 1.2U_{eq}$(carrier). Data collection: SMART (Bruker 2002); cell refinement: SAINT (Bruker 2002); data reduction: SAINT (Bruker 2002); program (s) used to solve structure: SHELXS97 (Sheldrick 1997); program (s) used to refine structure: SHELXL97 (Sheldrick 1997); molecular graphics: Ortep-3 for Windows (Farrugia 1997); software used to prepare material for publication: WinGX (Farrugia 1999).

Results and Discussion

The reported method for the synthesis of 3-nitromethylene-1,3-dihydro-indol-2-one derivatives was catalyzed by DBU in EtOH, and the yield was relatively low [1–3]. Based on the comparability of Aldol reaction and Henry reaction and the catalysis activity of diethylamine in Aldol reaction, diethylamine was introduced into the solvent-free reaction between isatin and nitromethane. Fortunately, the result proved to be effective. The reaction processed quickly, only few minutes was needed, and the yield was as high as near to 100%. Besides, it was so neat that it could be used to synthesize 3-nitromethylene-1,3-dihydro-indol-2-one directly avoiding a separation course.

Based on the mechanism of diethylamine catalyzed Aldol reaction, the mechanism of the reaction between isatin and nitromethane catalyzed by diethylamine was proposed and shown in Scheme 2. Initially, nitromethane (**A**) isomerizes to **B**, and then combines with diethylamine to form a hexahydroxy cycle intermediate **C**, which reacts



Scheme 2 The mechanism of the Henry reaction between isatin and nitromethane catalyzed by diethylamine

with isatin (**D**) proceeding transition state **E**. In this bimolecular complex **E**, the ammonium proton enables hydrogen bonding between the reaction partners. Several theoretical studies have highlighted the importance of the hydrogen bonds in this reaction [7–9]: it ensures the

Table 1 Experimental data

Empirical formula	$C_9H_8N_2O_4$
Formula weight	208.17
Temperature	273(2)
Wavelength (Mo K_α)	0.71073
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	10.515(2)
	7.3736(14)
	23.261(4)
Volume	1,803.6(6)
Z	8
Density (calculated)	1.533 mg/m^3
Absorption coefficient	0.123
F (000)	864
Crystal size	0.21 × 0.18 × 0.15 mm^3
Theta range for data collection (°)	1.8–34.3
Index ranges	$-12 \le h \le 12$; $-9 \le k \le 11$; $-28 \le l \le 36$
Reflections collected	3,007
Independent reflections	2,098
Reflections theta (°)	1.75–34.30
Absorption correction transmission	0.9407–0.9608
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3,007/0/136
Goodness-of-fit on F^2	1.034
Final *R* indices [$I > 2s(I)$]	$R1 = 0.0683$; $wR2 = 0.1347$
R indices (all data)	$R1 = 0.0452$; $wR2 = 0.1204$
Refine different density	−0.209–0.308

Table 2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$)

Atom	*x*	*y*	*z*	U*eq*
N1	7,379.3(10)	2,253.6(14)	5,957.5(4)	345(2)
H1A	8,121	2,684	5,882	41
C7	6,887 (11)	2,032 (15)	6,518.3(5)	313(3)
C8	5,674.4(11)	1,289.8(14)	6,488.7(5)	294(2)
C2	5,321.1(11)	1,026.2(14)	5,867.7(5)	287(2)
O1	6,714 (9)	1,657.4(14)	5,034.6(4)	452(3)
C3	5,008.7(12)	8,802(17)	6,984.4(5)	374(3)
H3A	4,196	6,966	386	45
C9	4,122.1(12)	2,058 (16)	5,682.8(5)	354(3)
H9A	4,059	2,048	5,267	43
H9B	3,377	1,453	5,837	43
C6	7,460.9(13)	2,426.8(17)	7,038 (5)	39.6(3)
H6A	8,264	2,951	7,055	48
N2	4,152.4(12)	3,958.6(15)	5,889.4(5)	47 (3)
C5	6,783.2(15)	2,004.9(18)	7,533.6(6)	45 (3)
H5A	7,145	2,253	7,890	54
C4	5,587.2(14)	1,227(2)	7,512.3(5)	44.8(3)
H4A	5,167	934	7,852	54
O3	5,050.8(14)	4,884.3(17)	5,745 (9)	90.4(5)
O4	3,288.1(14)	4,482.7(19)	6,194.1(6)	77.6(4)
C1	6,539.4(11)	1,704.4(15)	5,554.5(5)	31.7(3)
O2	5,162.1(8)	−841.4(11)	5,741.4(4)	39.1(2)
H2A	4,586	−966	5,507	59

Table 3 Selected bond lengths (Å) and angles (°)

Bond	Dist.	Bond	Dist.
N1 C1	1.3500(16)	N1 C7	1.4130(16)
C7 C6	1.3822(17)	C7 C8	1.3893(17)
C8 C3	1.3823(17)	C8 C2	1.5042(15)
C2 O2	1.4180(13)	C2 C9	1.5340(16)
C2 C1	1.5563(16)	O1 C1	1.2237(14)
C3 C4	1.3940(19)	C9 N2	1.4819(17)
C6 C5	1.391(2)	N2 O4	1.2155(18)
N2 O3	1.2130(19)	C5 C4	1.383(2)
Angle	(°)	Angle	(°)
C1 N1 C7	111.51(10)	C6 C7 C8	121.81(11)
C6 C7 N1	128.55(11)	C8 C7 N1	109.63(10)
C3 C8 C7	120.63(11)	C3 C8 C2	130.37(11)
C7 C8 C2	108.98(10)	O2 C2 C8	110.71(9)
O2 C2 C9	109.07(9)	C8 C2 C9	114.09(9)
O2 C2 C1	108.19(9)	C8 C2 C1	101.81(9)
C9 C2 C1	112.70(9)	C8 C3 C4	118.27(12)
N2 C9 C2	111.13(9)	C7 C6 C5	117.02(12)
O4 N2 O3	124.39(14)	O4 N2 C9	118.28(14)
O3 N2 C9	117.33(13)	C4 C5 C6	121.94(12)
C5 C4 C3	120.30(12)	O1 C1 N1	126.62(11)
O1 C1 C2	125.24(10)	N1 C1 C2	108.05(10)

Table 4 Hydrogen bond geometry (Å, and °)

D–H···A	D–H	H···A	D···A	D–H···A
N(1)–H(1A)···O(2)	0.86	2.13	2.9833(17)	171
O(2)–H(2A)···O(1)	0.82	1.92	2.7396(16)	171
O(5)–H(5B)···O(3)	0.97	2.42	2.383(2)	170

Symmetry codes: $-x + 1/2, -y, z + 1/2$; $-x, y + 1/2, -z + 1/2$; $x + 1/2, -y + 1/2, -z$

incoming of isatin; it lowers the activation barrier of the reaction by charge stabilization along the C–C bond formation. During the transition state **E**, by a series of electrons transfer, a proton transfers from the ammonium to the oxygen anion, the desired adduct (3-nitromethylene-1,3-dihydro-indol-2-one, **F**) is formed, and diethylamine is released into another catalysis cycle.

In order to provide the structural information of compound **1**, we studied its crystal structure by single crystal X-ray diffraction in the following research. The main data is displayed from Tables 1, 2, 3 and 4. The molecular structure is shown in Fig. 1, the intermolecular hydrogen bonds and a packing diagram are depicted in and Figs. 2 and 3, respectively. The X-ray structural determination of **1** confirmed the assignment of its structure from NMR and MS spectra data.

Geometric parameters of the title compound (**1**) are in the usual ranges. It crystallizes in the orthorhombic space group, Pbca, with unit cell dimensions $a = 10.515$ (2) Å, $b = 7.3736$ (14) Å, and $c = 23.261$ (4) Å. The two rings are coplanar, and the angle between hydroxyl group and the nitromethyl group is 109.07(9)°. In the crystal structure, intermolecular N–H···O and O–H···O hydrogen bonds (Table 4) seem to be effective in the stabilization of the structure, which are primarily responsible for the formation of the framework (Fig. 2). The N and O of nitro group are not involved in any hydrogen bond. There is no intramolecular hydrogen bond. In the crystal, the non-polar parts, phenyls, pack together by π–π stacking, while the polar parts are fixed one another by intermolecular hydrogen bonds. The molecules are oriented layer by layer by the interactions as shown in Fig. 3.

Supplementary Material

Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic

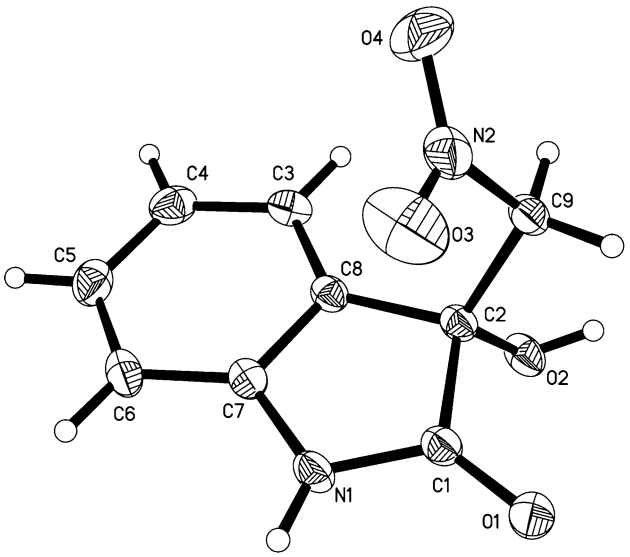


Fig. 1 The molecular structure of the title molecule

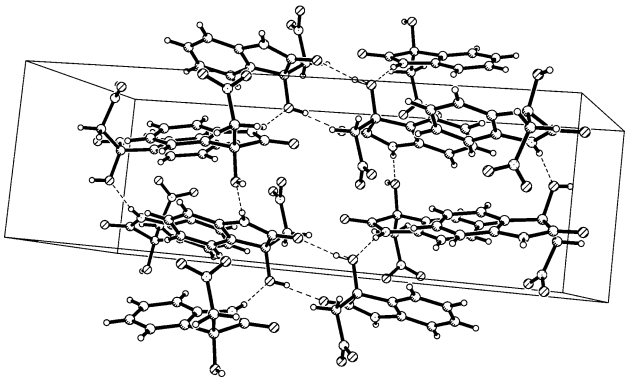


Fig. 2 The intermolecular hydrogen bonds in the crystal

Data Center. Copies of the data (CCDC-698198) can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [E-mail: deposit@ccdc.cam.ac.uk].

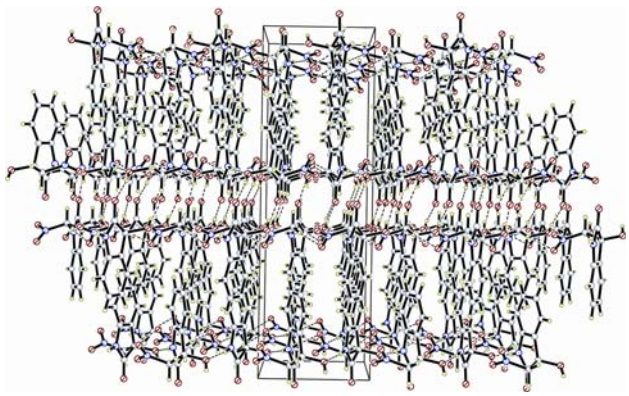


Fig. 3 A packing diagram of the title molecular

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