Crystal Structure and New Approach to Spiro[1,3-dioxolane-2,3'-indolin]-2'-one

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ABSTRACT:

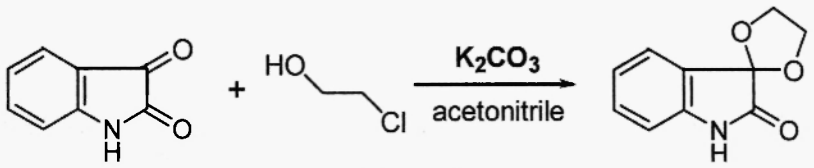
The title compounds, spiro[1,3-dioxolane-2,3'-indolin]-2'-one, was synthesized with isatin and 2-chloroethanol by a intramolecular substitution reaction in the presence of K_2CO_3 for the first time, which avoided the using of H^+ as catalyst in traditional synthesis of ketal compounds. The structure of spiro[1,3-dioxolane-2,3'-indolin]-2'-one was studied by X-ray single crystal diffraction, and the two byproducts in the reaction were characterized by H^1-NMR, MS spectrums. With these results, the proposed way to spiro[1,3-dioxolane-2,3'-indolin]-2'-one and the two byproducts was brought forward.

Keywords:, isatin, 2-chloroethanol, spiro[1,3-dioxolane-2,3'-indolin]-2'-one, intermolecular substitution reaction.

INTRODUCTION

Isatin, as well as its derivatives, has caught great attention of many researchers as a versatile lead molecule for designing of potential drugs for the variety of biological activities, such as anti-bacteria, anti-virus, anti-tumor and neuroprotection.[1-4] Among these compounds, spiro [pyrrolidine-2,3'-oxindoline] analogues have received considerable attention as potential anti-bacteria and neuroprotection agents.[5-7] Further research reveals that its neuroprotection properties are not only maintained but become even more pronounced after the transformation to its β-ethylene ketals. 1-Substituted-spiro[1,3-dioxolane-2,3'-indolin]-2'-ones have been synthesized and found to be potent as an anxiolytic, and 1-[(4-bromophenyl)-2-oxoethyl]-spiro[1,3-dioxolane-2,3'-indolin]-2'-one has the most potent anxiolytic effect, exceeding that of medazepam.[5]

In the traditional way, the synthesis of glycol acetals / ketals is catalyzed by strong acid to afford glyeol–H^+ intermediates in benzene or cyclohexane. In this reaction, the generated water must be separated by a water separator to promote the condensation reaction.[5,8] In this paper, we will report a new simple way to synthesize spiro[1,3-dioxolane-2,3'-indolin]-2'-one with isatin and 2-chloroethanol by intermolecular and intramolecular substitution reaction in the presence of K_2CO_3 (as shown in **Scheme 1**).

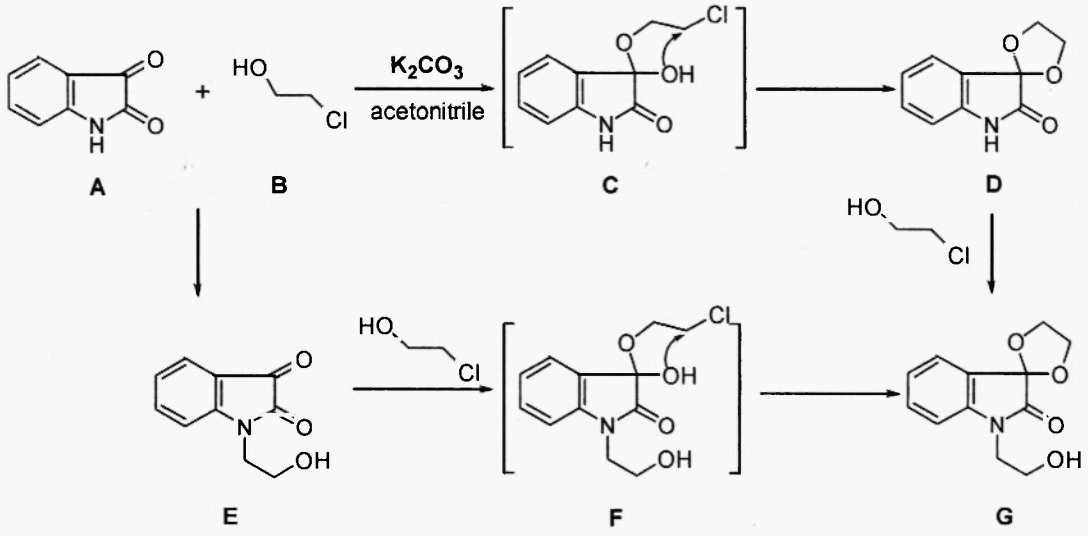


Scheme 1

RESULTS AND DISCUSSION

In our experiment, 2-chloroethanol was introduced into the synthesis of spiro[1,3-dioxolane-2,3'-indolin]-2'-one. Isatin and 2-chloroethanol was dissolved in acetonitrile and anhydrous K_2CO_3 was added as a promoter. After the reaction finished, the target products was gotten with high yield, and afford two byproducts, which could be due to the side reactions as shown in Scheme 2. All of the products were characterized by H^1-NMR and MS spectrums, and they were determined as spiro[1,3-dioxolane-2,3'-indolin]-2'-one (**D**), 1-(2-hydroxyethyl)-indol-2,3-dione (**E**) and 1-(2-hydroxyethyl)-spiro[1,3-dioxolane-2,3'-indolin]-2'-one (**G**). The reaction process was proposed as the following **Scheme 2**. In the reaction, the hydroxyl group of 2-chloroethanol (**B**) attacked to the carbonyl of isatin (**A**) and formed a hemiketal intermediate (**C**), and then an intramolecular substitution reaction occured: the hydroxyl group of the hemiketal attack to the α-carbon atom of the chloro atom, as the leaving of chlorion, the ketal was formed. Compound **E** produced by a N-substitution reaction of isatin and 2-chloroethanol, and compound **G** maybe produced in a condensation reaction of **E** and 2-chloroethanol or a N-substitution reaction of **D** and 2-chloroethanol. The two approaches to synthesis compound **G** were proceeded in our following works successfully.

In a common sense, the addition of hydroxyl group to carbonyl should be catalyzed by a strong acid, such as HCl or H_2SO_4, but in this reaction only anhydrous K_2CO_3 was in presence, while the reaction went through swimmingly. The reason might be as follows: the carbonyl group of isatin is activated by the α-acyl group; on the other hand, the intramolecular substitution of hydroxyl group to α-carbon atom of the chloro atom will generate an equivalent of HCl, as a solid base, K_2CO_3 can promote the leaving of the generated HCl molecules in the last step, which accelerates the whole process, and high yield was achieved at the same time. Another important role of this result is its potential application in the synthesis of acetals / ketals with the acid sensitive substrate.



Scheme 2 The reaction between isatin and 2-chloroethanol in the presence of K_2CO_3.

The structure of spiro[1,3-dioxolane-2,3'-indolin]-2'-one was further studied by X-ray single crystal diffraction, and the ORTEP-3 drawing, the dimer unit and the packing of the title compound were shown in **Figure 1-3**. The X-ray structural analysis confirmed the assignment of its structure from spectroscopic data. Geometric parameters of the title compound are in the usual ranges. Although the conjugative system was destroyed by the addition reaction of carboxyl group with 2-chloroethanol, the indol-2-one moiety is still planar. The five-membered 1,3-dioxolane displays a classical envelop conformation, O2, C2, O3 and C10 form the face of the envelop in a unsubstantially planar. In the crystal structure, two title compounds connect with each other to form a dimer by the intermolecular N1-H1A...O1 hydrogen bonds, the distance of hydrogen bond donor and accepter is 2.939(5)Å., and the angle of the hydrogen bond is 170°. The other two O atoms aren't involved in any hydrogen bonds. The distance between indol-2-one moieties is 4.5675(17) to 4.8976(18)Å., and the weak π-π stacking between the plans are responsible for the formation of the framework.

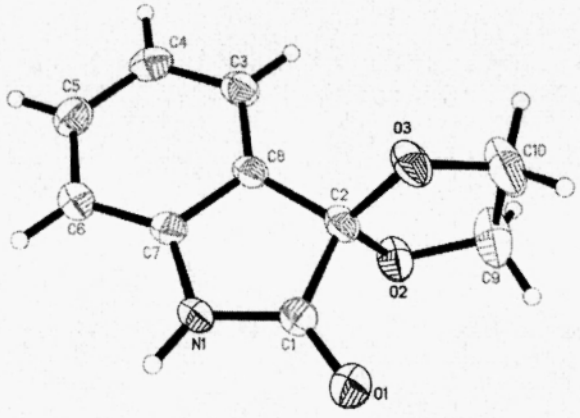


Fig. 1: The ORTEP-3 drawing of spiro[1,3-dioxolane-2,3'-indolin]-2'-one.

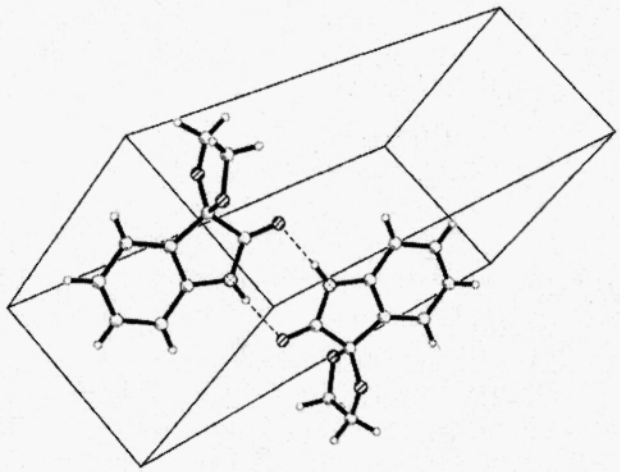


Fig. 2: The hydrogen bonds between spiro[1,3-dioxolane-2,3'-indolin]-2'-one.

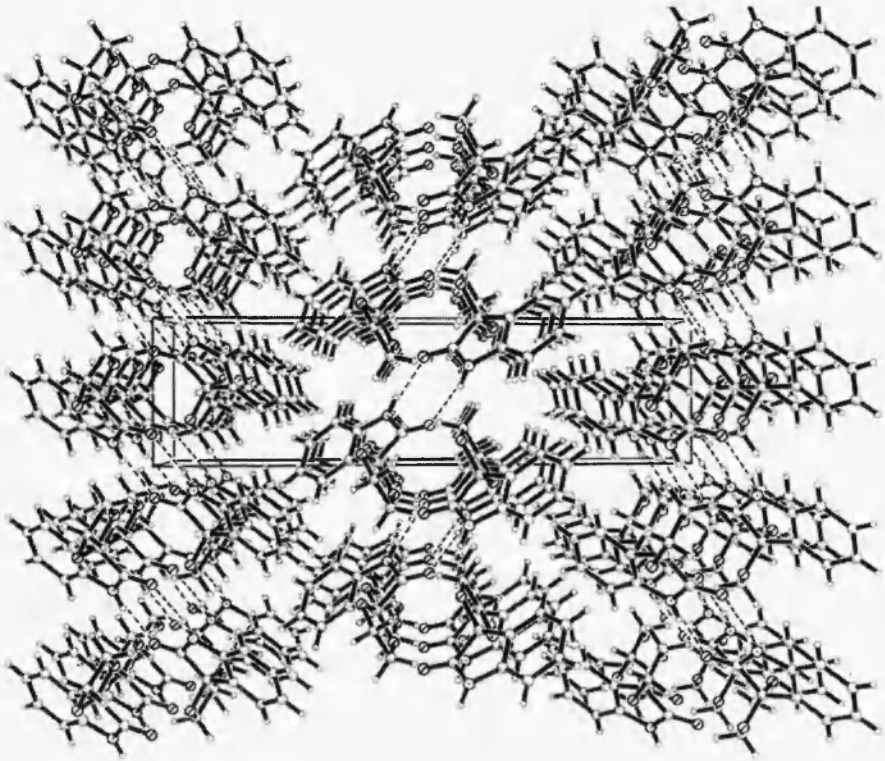


Fig. 3: The packing of spiro[1,3-dioxolane-2,3'-indolin]-2'-one.

EXPERMENTAL

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

1.5 g isatin was dissolved 30 ml acetonitrile, 3 g K_2CO_3 and 0.9 g 2-chloroethanol were added. The mixture was stirred over night at room temperature, and the color of the mixture turned to yellowish from orange. On complete reaction, K_2CO_3 was filtered, and washed with acetonitrile. The solvent was evaporated in vacuum to 20mL and the residue was cooled. The product was filtered to give colorless crystals of **D**. Additional amounts of product **D** as well as **E** and **G** were obtained from the mother liquor by a column chromatogram separation.

spiro[1,3-dioxolane-2,3'-indolin]-2'-one (**D**), yield 81%: ^{1}H-NMR (D_6-DMSO, 400MHz), δ: 10.44 (1H, s), 7.33 (2H, m), 7.0 (1H, td, *J* = 7.2, 0.8 Hz), 6.82 (1H, d, *J* = 7.6 Hz), 4.33 (2H, m), 4.23 (2H, m); ^{13}C-NMR (D_6-DMSO, 100MHz), δ: 65.9, 102.5, 110.8, 123.2, 124.3, 125.0, 131.7,141.8, 175.9. MS (EI) *m/z*: 233 (M^+)

1-(2-hydroxyethyl)-indol-2,3-dione (**E**), yield 7%: ^{1}H-NMR (D_6-DMSO, 400MHz), δ: 7.56 (1H, td, *J* = 1.2, 8 Hz), 7.54 (1H, d, *J* = 7.6 Hz), 7.20 (1H, d, *J* = 8), 7.14 (1H, t, *J* = 7.6 Hz), 4.87 (1H, t, *J* = 6 Hz), 3.74 (2H, t, *J* = 5.6 Hz), 3.62 (2H, m, *J* = 5.6-6 Hz); MS (EI) *m/z*: 191 (M^+).

1-(2-hydroxyethyl)-spiro[1,3-dioxolane-2,3'-indolin]-2'-one (**G**), yield 8%: ^{1}H-NMR (D_6-DMSO, 400MHz), δ: 7.38 (2H, m), 7.07 (2H, m), 4.89 (1H, t, *J* = 5.6 Hz), 4.35 (2H, m), 4.26 (2H, m), 3,63 (2H, m), 3,56 (2H, m); MS (EI) *m/z*: 233 (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).

The experimental data is reported in **Table 1-3**. The main information of the crystal was shown in **Table** 4.

Table 1

The crystal data.

Crystal data	
$C_{10}H_9NO_3$	F(000) = 396
Mr = 191.18	Dx = 1.466 Mg m^{-3}
Monoclinic, P21/c	Mo Kα radiation, λ = 0.71073 Å
a = 7.4838 (18) Å	Cell parameters from 7304 reflections
b = 5.6502 (14) Å	θ = 1.5–25.0°
c = 20.941 (5) Å	μ = 0.11 mm^{-1}
β = 97.889 (8)°	T = 273 (2) K
V = 877.1 (4) $Å^3$	0.36 × 0.27 × 0.21 mm
Z = 4	Block, colorless

Table 2

The data collection of the analysis.

Data collection	
Bruker SMART CCD diffractometer	phi and ω scans
Absorption correction: multi-scan (SADABS; Bruker, 2001)	Rint = 0.072
T_{min} = 0.963, T_{max} = 0.989	θ_{max} =30.2°, θ_{min} = 2.0°
5101 measured reflections	$h = -9 \rightarrow 10$
2539 independent reflections	$k = -7 \rightarrow 7$
1246 reflections with I > 2σ(I)	$l = -23 \rightarrow 28$

Table 3

The refinement of the structure.

Refinement	
Refinement on F^2	Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.054$	Hydrogen site location: inferred from neighbouring sites
$wR(F^2) = 0.182$	$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.02$	$(\Delta/\sigma)max = 0.045$
2139 reflections	$\Delta\rho max = 0.21$ e $Å^{-3}$
127 parameters	$\Delta\rho min = -0.25$ e $Å^{-3}$
Primary atom site location: structure-invariant direct methods	Secondary atom site location: difference Fourier map

Table 4

Bond lengths (Å) and bond angles(°)

O1—C1	1.223 (2)	C3—C4	1.397 (3)
O3—C2	1.398 (2)	C3—H3A	0.9300
O3—C10	1.387 (3)	C6—C5	1.389 (3)
O2—C2	1.422 (3)	C6—H6A	0.9300
O2—C9	1.386 (3)	C5—C4	1.366 (3)
N1—C7	1.405 (2)	C5—H5A	0.9300
N1—C1	1.350 (3)	C4—H4A	0.9300
N1—H1A	0.8600	C10—C9	1.450 (4)
C7—C8	1.386 (3)	C10—H10A	0.9700
C7—C6	1.383 (3)	C10—H10B	0.9700
C2—C8	1.505 (3)	C9—H9B	0.9700
C2—C1	1.549 (3)	C9—H9C	0.9700
C8—C3	1.377 (3)		
C2—O3—C10	109.00 (19)	C5—C6—H6A	121.4
C2—O2—C9	108.72 (19)	O1—C1—N1	126.6 (2)
C7—N1—C1	111.73 (19)	O1—C1—C2	125.9 (2)
C7—N1—H1A	124.1	N1—C1—C2	107.43 (17)
C1—N1—H1A	124.2	C4—C5—C6	121.7 (2)
N1—C7—C8	109.93 (17)	C4—C5—H5A	119.2
N1—C7—C6	128.3 (2)	C6—C5—H5A	119.2
C8—C7—C6	121.81 (19)	C5—C4—C3	120.6 (2)
O2—C2—O3	107.18 (16)	C5—C4—H4A	119.7
O2—C2—C8	111.72 (16)	C3—C4—H4A	119.7
O3—C2—C8	115.34 (17)	C9—C10—O3	107.4 (2)
O2—C2—C1	109.09 (17)	C9—C10—H10A	110.4
O3—C2—C1	111.16 (17)	O3—C10—H10A	110.3
C8—C2—C1	102.25 (16)	C9—C10—H10B	110.0
C3—C8—C7	120.10 (19)	O3—C10—H10B	110.2
C3—C8—C2	131.7 (2)	H10A—C10—H10B	108.5
C7—C8—C2	108.23 (16)	C10—C9—O2	106.3 (2)
C8—C3—C4	118.6 (2)	C10—C9—H9B	110.7
C8—C3—H3A	120.6	O2—C9—H9B	110.6
C4—C3—H3A	120.8	C10—C9—H9C	110.3
C7—C6—C5	117.3 (2)	O2—C9—H9C	110.3
C7—C6—H6A	121.4	H9B—C9—H9C	108.6

ACKNOWLEDGMENTS

This work was financially supported by the grants from Scientific Research Foundation for PhD of Xi'an Shiyou University (Z08008), Natural Science Research Plan Projects of Shaanxi Science and Technology Department (SJ08B20) and Scientific Research Plan Projects of Shaanxi Education Department (09JK702).

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