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Preparation of dibarbiturates of oxindole by condensation of isatin and barbituric acid derivatives

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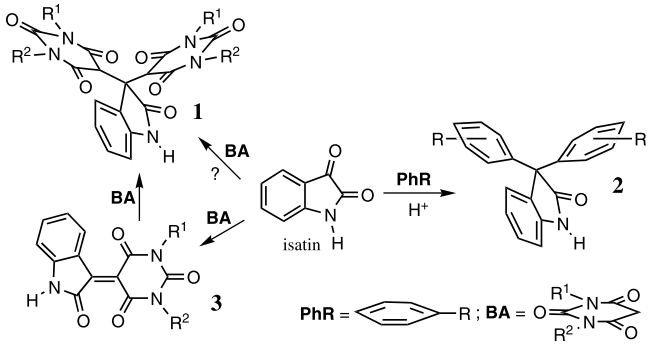
Abstract—A very efficient, simple, and high yield procedure for the isatin condensation with barbituric acid derivatives was described. The condensation reaction is very selective, which is corroborated by following the reaction by NMR, and the structure of the product was confirmed by X-ray structural analysis.

Oxindole derivatives with 3,3-diaryl groups have been shown to have antibacterial, antiprotozoal, and anti-inflammatory activities.[1] Surprisingly, there are no literature references to biological activity of their barbituric acid analogs (compound **1**, Scheme 1). This might be due to the lack of availability of these compounds. To the best of our knowledge there are no literature data for preparation of derivatives of isatin-barbiturates **1**. There is, however, an abundance of literature information in regards to the preparation of 3,3-diaryloxindoles **2**. The usual route for the preparation of **2** is by acid-catalyzed aryl-isatin condensation.[2,3] One can assume that a similar synthetic approach might be applicable for the preparation of barbituric acid analogs **1**.

There are many difficulties associated with this synthetic approach. Even for the preparation of **2** from isatin and moderately reactive aromatic compounds, forceful reaction conditions are required.[3] For instance, if **2** (R = H) is to be obtained in preparative yield through isatin condensation with benzene then a reaction media with an acid strength of more than $H_o = -11.5$ is required (a mixture of CF_3SO_3H and CF_3CO_2H).[3] These are rather drastic reaction conditions that might decompose both barbituric acid and compound **1**. The study of isatin condensation with barbituric acid was performed previously.[4] It was reported that the condensation of isatin with barbituric acid in a mixture of glacial acetic acid and acetic anhydride generates condensation product **3**. One can then speculate that compound **1** can be prepared through the Michael-type (strong base-catalyzed) barbituric acid addition to **3** (Scheme 1).

As a first step in the preparation of **1** we explored the most suitable reaction conditions for quantitative transformation of isatin and barbituric acid into **3**. When an equimolar methanol or acetic acid solution of isatin and barbituric acid was heated, only 50% of isatin was converted into a white solid material for which spectroscopic data (^1H and ^{13}C NMR, and X-ray structural analysis) agree with the structure of our target molecule **1**, but not **3**. This was a quite surprising finding so we decided to perform the NMR reaction following experiments in CD_3CO_2D, CD_3OD, CD_3ONa/CD_3OD, CD_3OD with a drop of H_2SO_4, and CD_3SOCD_3. It is obvious that the only condensation product is **1a** regardless of the reactants molar ratio (Fig. 1).[5] At the same time, the NMR experiments demonstrate that conversion into **1a** is quantitative; therefore, this reac-



Scheme 1. Two possible products (**1** and **3**) of isatin condensation with barbituric acid.

Keywords: barbituric acid; isatin; oxindole; condensation reactions; isatin-dibarbiturates.

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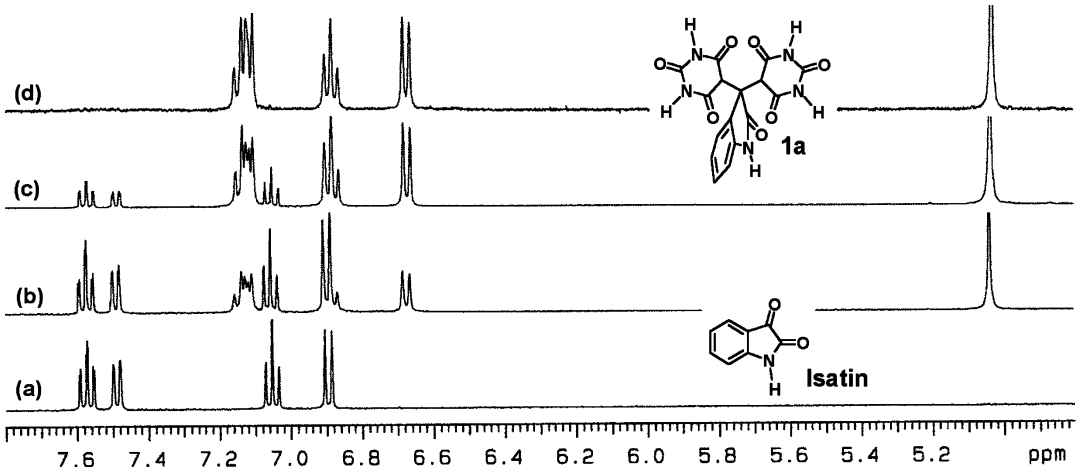

Figure 1. The ^{1}H NMR reaction monitoring in DMSO, (a) isatin, (b) reaction after 5 days, (c) after 36 days, and (d) after 90 days.

tion might be used as a preparation method to obtain **1** in both high purity and large quantity. At room temperature the reaction is relatively slow (90 days for reaction completion in DMSO) but in the refluxing methanol the reaction is practically over in few hours.

This approach is general and can be applied to aliphatic and aromatic barbituric acids although the rates of the reactions vary with the nature of barbituric acid (Fig. 2). Thus, 50% reaction conversion for the products barbituric acid (b), 1,3-dimethylbarbituric acid (c), and 1-phenylbarbituric acid (d) are accomplished in 5, 8, and 13 days respectively, at room temperature in DMSO-d_6 as a reaction media (Fig. 2).

Preparation of these compounds can be obtained in a highly concentrated refluxing methanol suspension. During the course of the reaction, the reaction mixture proceeds from a suspension of the reactants to a clear reaction solution, and then finally to a suspension of product **1** in methanol. Isolation involves simple filtration of the reaction mixture. Further purification of the product is not necessary but it can be performed by crystallization from a large amount of methanol. Isolated yields for some isatin-dibarbiturates **1** are presented in Table 1.[6]

To confirm the structure of the isatin-dibarbituric acid determined through spectroscopic studies, single-crystal X-ray study[7] of isatin-dibarbiturate **1b** obtained from crystallization from methanol was carried out. The structure has some unique properties (Fig. 3). Due to strong π–π interactions between barbituric acid and the indole moieties of **1b** in the crystal packing, two of the of the dimethylbarbituric acid rings are not identical. That makes the C3 carbon chiral and two molecules of **1b** cocrystallize as a racemic pair. Another feature is

Table 1. Isolated yields of isatin-dibarbiturates **1**[6]

Compound	R^1	R^2	Yield (%)
1a	H	H	91
1b	CH_3	CH_3	95
1c	H	CH_3	84
1d	H	$(CH_2)_3CH_3$	97
1e	H	C_6H_5	95
1f	H	3-HOC_6H_4	84

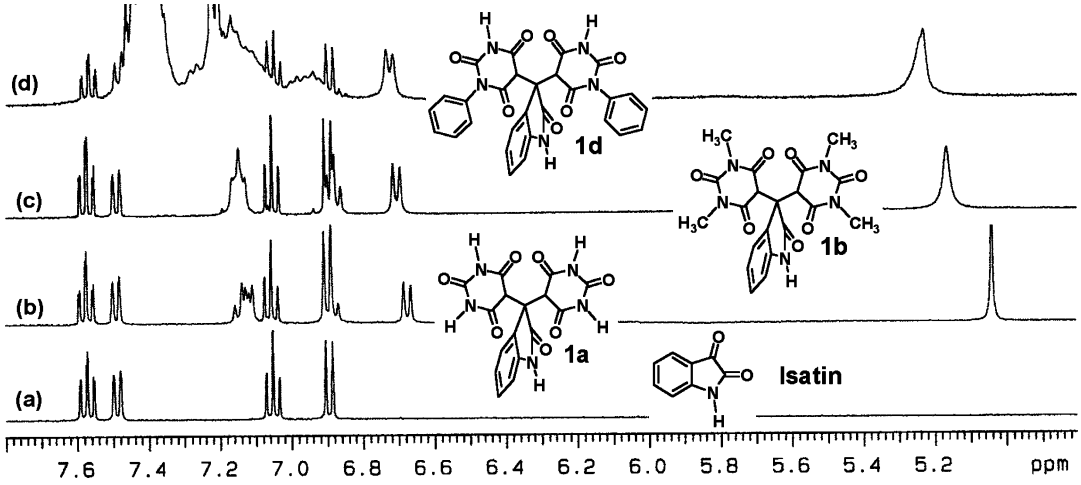

Figure 2. The NMR spectra of the reaction mixture when ~50% product is formed, (b) 5 days, (c) 8 days, (d) 13 days.

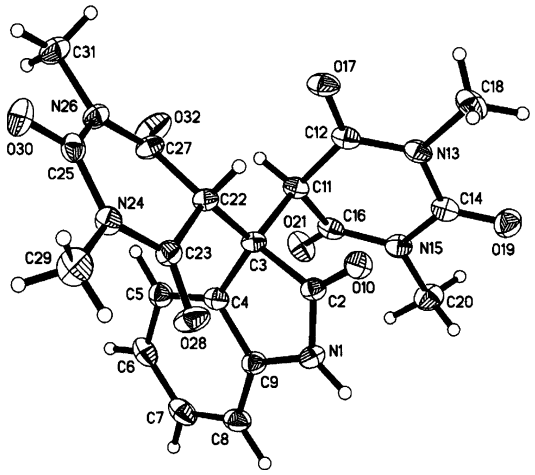

Figure 3. ORTEP of X-ray structure of **1b** and space filing X-ray structure of the **1b** dimer.

that hydrogen bonding between the hydrogen attached to C11 and oxygen O32 as well as hydrogen attached to C22 and oxygen O17 are evident. These interactions define the shape of the molecule.

Acknowledgements

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5. The ^{1}H NMR reaction monitoring was performed in DMSO-d_6 (1 ml) with isatin (1.5 mg; 10 μM) and barbituric acid (2.56 mg; 20 μM) at room temperature on a Varian INOVA 500 MHz NMR spectrophotometer. The ^{1}H and ^{13}C NMR data for 5,5′-(2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**1a**) in this reaction following experiments are: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.195 (4H, s, NH), 10.547 (1H, s, NH), 7.148 (1H, t, $J=7.8$ Hz), 7.135 (1H, d, $J=7.8$ Hz), 6.895 (1H, t, $J=7.8$ Hz), 6.703 (1H, t, $J=7.8$ Hz) and 5.053 ppm (2H, s, CH); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 172.439, 164.233, 146.963, 139.850, 125.632, 124.751, 120.979, 118.280, 106.294, 50.260, and 47.489 ppm.
6. Typical procedure for the preparation of isatin-dibarbiturate **1** as demonstrated on the example of preparation of 5,5′-(2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)bis(1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (**1b**) is as follows: Methanol (100 ml) suspension of isatin (5.89 g, 0.04 mol) and 1,3-dimethylbarbituric acid (12.5 g; 0.08 mol) was refluxed for 5 h (after ~15 min reaction mixture became solution and after ~40 min it again became suspension). The white solid was separated by filtration washed with methanol (3×20 ml) and dried on the air to afford 16.7 g (94.6%) of pure **1b**. Elemental analysis for $C_{20}H_{19}N_5O_7$ (FW 441.39) calcd C, 54.42; H, 4.34; N, 15.87. Found C, 54.29; H, 4.46; N, 15.75%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.599 (1H, s, NH), 7.148 (1H, t-d, $J_1=7.5$ Hz, $J_2=1.2$ Hz), 7.145 (1H, d, $J=7.5$ Hz), 6.877 (1H, t-d, $J_1=7.5$ Hz, $J_2=1.2$ Hz), 6.722 (1H, d, $J=7.8$ Hz) 5.148 (2H, s, CH), 3.032 (6H, s, CH_3), and 2.974 ppm (6H, s, CH_3); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 172.408, 162.487, 147.904, 139.740, 125.886, 123.719, 121.719, 118.401, 106.199, 51.065, 48.506, 24.985, and 24.518 ppm.
7. X-Ray structure determination was performed on a Bruker SMART 1KCCD automated diffractometer. Crystals of compound **1b** were obtained by crystallization from methanol by allowing slow solvent evaporation. All reagents and solvents were purchased from Aldrich and used without prior purification. X-Ray single-crystal structure determination of compound **1b** at 150(2) K.
Crystal data: $C_{20}H_{19}N_5O_7$, $M_r=441.40$, monoclinic, space group $P2_1/n$, $a=10.5838(3)$, $b=29.0894(7)$, $c=12.9131(2)$ Å, $\alpha=90.0$, $\beta=97.3440(10)$, $\gamma=90.0°$, $V=3943.02(15)$ Å^3, $Z=8$, ρ_{calcd} 1.487 Mg m^{-3}, $F_{000}=1840$, wavelength (λ)= 0.71073 Å, absorption coefficient (μ)=0.115 mm^{-1}.
Data collection and reduction: Crystal size: 0.3×0.4×0.6 mm, Theta range: 1.74–30.00°, index ranges: $-14\leq h\leq 14$, $-40\leq k\leq 40$, $-18\leq l\leq 18$, reflections collected/unique 48765/11483 [$R_{int}=0.0373$], refinement method: full-matrix least-squares on F^2, data/restraints/parameters: 11483/182/730. Final R indices [$I>2\sigma(I)$]: $R_1=0.0505$, $wR_2=0.0823$, goodness-of-fit on F^2: 1.226 R indices (all data) $R_1=$ 0.0518, $wR_2=0.0818$, largest diff. peak and hole: 0.389 and −0.350 e Å^{-3}.
Measurement, computing and graphics: SMART 1K CDD (Bruker, 2000); cell refinement: SMART; data reduction SAINT-Plus (Bruker, 2000); programs(s) used to solve structure: SHELXS-97 (Sheldrick, 1997); program(s) used to refine structure: SHELX-97 (Sheldrick, 1997); molecular graphics: SHELXTL-97 (Sheldrick, 1997); software used to prepare material for publication: SHELXTL-97.
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