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Full Paper

DABCO Promoted Regioselective Synthesis of New Diversely Functionalized 3-Hydroxy-2-Oxindole Scaffolds

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An efficient and highly regioselective γ-addition of β-keto sulfones on isatins has been achieved in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) to afford a γ-(3-hydroxy-2-oxindole)-β-keto sulfone structural framework. The scope of the method is tested by screening a series of isatin electrophiles as well as β-keto sulfones. The described method was found to be very handy and provides straightforward access for the diversely functionalized 3-β-keto sulfone substituted-3-hydroxy-2-oxindole structural scaffolds in very good yields from readily available starting materials under metal-free reaction conditions.

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Introduction

The alkaloid class of natural products and pharmaceuticals, in particular the 3-substituted 3-hydroxy-2-oxindoles, possesses a large array of biological activities.[1] As a result of the prevalence of the 3-substituted 3-hydroxy-2-oxindole framework, it remains a highly investigated synthetic target for worldwide chemists (Fig. 1). In addition to this, organosulfones show a wide range of bioactivities such as antibacterial, antiparasitic, DNA cleavage, anti-HIV, antiviral, and antiandrogen.[2–4] A specific example is the well known drug Bicalutamide, an oral non-steroidal antiandrogen that possesses a sulfonyl functionality (Fig. 1). Because of the prominence of 3-hydroxy-2-oxindole and organosulfone structural motifs in the biological arena, the synthesis of 3-hydroxy-2-oxindoles having an organosulfone framework is highly desirable from a medicinal chemistry point of view.

The direct addition of a nucleophile[5–10] to isatin is a very common approach used for the synthesis of this framework as the β-carbonyl group of isatin is highly susceptible to nucleophilic attack.[11] In this context, we focussed our attention on β-keto sulfones,[12–14] which have been explored in many nucleophilic addition reactions[15] and affords α-addition products. Alternately β-keto sulfones undergo regioselective γ-addition with aldehydes to give γ-hydroxy-substituted β-keto sulfone frameworks using a dianion method.[16]

Recently we reported that 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed the highly regioselective γ-addition reaction of β-keto esters on isatin to afford γ-(3-hydroxy-2-oxindole)-β-keto ester structural frameworks.[17a] In this context we intend to study DABCO as a catalyst for the γ-addition reaction of β-keto sulfones with isatin. Although one example of a γ-addition reaction of a β-keto sulfone on isatin has been reported,[17b] no detailed study specially focussed on the reactions of β-keto sulfones with isatin in the presence of DABCO appears in the literature. In this regard, and as a part of our effort towards the synthesis of new 3-substituted 3-hydroxy-2-oxindoles,[18] we herein report the DABCO catalyzed highly regioselective γ-addition of β-keto sulfones to isatins for the synthesis of β-keto sulfone substituted 3-hydroxy-2-oxindole frameworks (entry 3, Scheme 1).

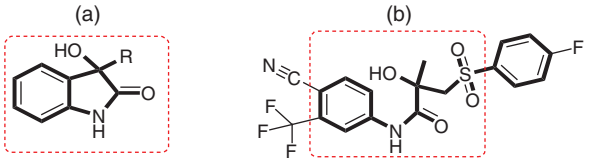


Fig. 1. (a) Representation of the bioactive 3-substituted-3-hydroxy-2-oxindole structural framework and (b) the drug Bicalutamide containing the organosulfone structural framework.

Results and Discussion

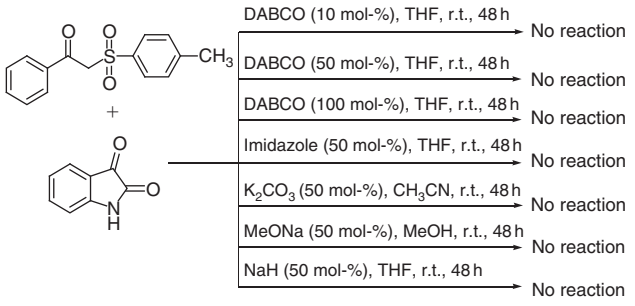
As part of our persistent interest in 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed reactions,[18c,19] we intended to investigate the potential of DABCO in the reaction of β-keto sulfones with isatin. As a model reaction, initially we attempted the reaction of 1-(phenylsulfonyl)propan-2-one with isatin in THF in the presence of 10 mol-% DABCO (Scheme 2). The reaction proceeded to afford the new product as a white solid.

Both crude and pure products were subjected to ^{1}H NMR analysis. By the extensive analysis of ^{1}H NMR spectroscopic data, we elucidated the formation of the γ-addition product **3a** as the sole product and did not observe the formation of the α-addition product **3a′** even in trace amounts. Thus, our results showed that the reaction of the β-keto sulfone 1-(phenylsulfonyl)propan-2-one with isatin in the presence of 10 mol-% DABCO affords a single regioisomer, i.e. γ-(3-hydroxy-2-oxindol)-β-keto sulfone (**3a**) instead of α-(3-hydroxy-2-oxindol)-β-keto sulfone (**3a′**).

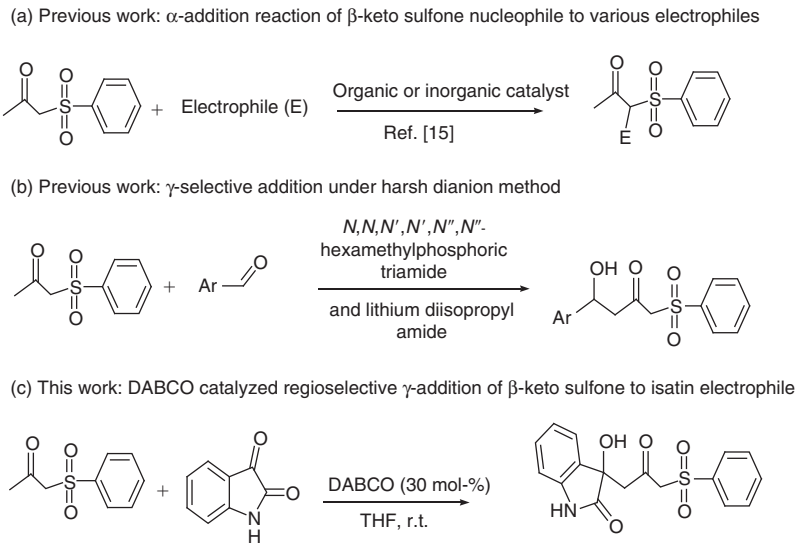
The observed γ-regioselectivity was also validated by an additional study (Scheme 3). When we performed the reaction of isatin with 2-[(4-methylphenyl)sulfonyl]-1-phenylethanone under different conditions, we did not observe the formation of a new product. These results clearly indicate that β-keto sulfones, having no enolizable proton at the γ-position, do not undergo an aldol reaction with isatin to give 3-β-keto sulfone substituted 3-hydroxy-2-oxindoles.

It is important to note that the reaction does not afford even a trace of the α-addition product under the screened reaction conditions. The γ-regioselectivity was also confirmed by independent synthesis of compound **3a** using the dianion method[16] (Scheme 4).

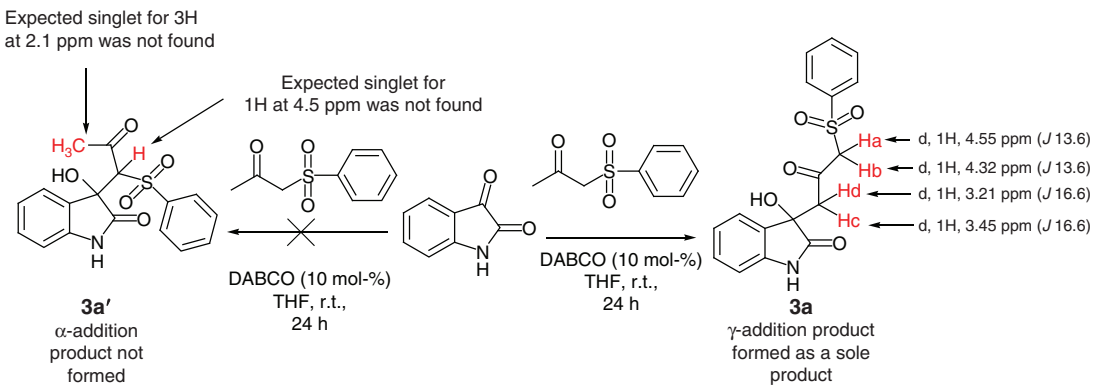
All the above experiments validate the formation of regioselective γ-(3-hydroxy-2-oxindole)-β-keto sulfone (**3a**). In the light of these studies, next we tested the scope of different catalysts for the aldol reaction of isatin with 1-(phenylsulfonyl) propan-2-one and the results are summarized in Table 1. It is worth noting that all screened catalysts have afforded only the regioselective γ-addition product **3a**. Subsequently, 30 mol-%



Scheme 3. Reaction of isatin with 2-[(4-methylphenyl)sulfonyl]-1-phenylethanone. Reaction conditions: isatin (1 mmol), β-keto sulfone (1 mmol) in 5 mL of solvent at room temperature.



Scheme 1. a, b) Selected reported reactions of β-keto sulfones with various electrophiles. c) Our present work with 1,4-diazabicyclo[2.2.2]octane (DABCO) at room temperature (r.t.).



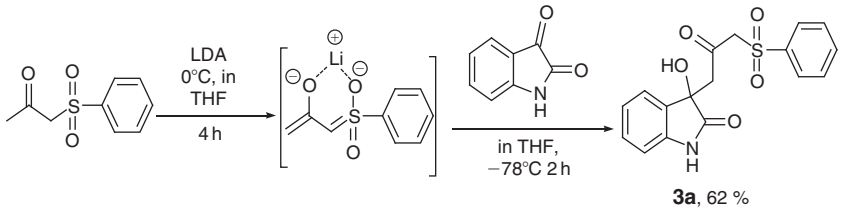
Scheme 2. Synthesis of β-keto sulfone substituted 3-hydroxy-2-oxindole frameworks using 1,4-diazabicyclo[2.2.2]octane (DABCO) at room temperature (r.t.).

DABCO in THF was ultimately favoured as the optimized reaction condition (entry 3, Table 1).

With optimum conditions in hand, we demonstrated the scope of the reaction with respect to various β-keto sulfones and isatins. To be specific, halogen-containing substrates such as 5-chloro isatin, 5-bromo isatin, and 5-iodo isatin as well as 1-(4-chlorophenylsulfonyl)propan-2-one were well tolerated and afforded desired products with complete regioselectivity in very good yields under optimized conditions (Table 2). The reaction of *N*-benzyl isatin with 1-(4-chlorophenylsulfonyl) propan-2-one also afforded a good yield of the desired product (Table 2, **3j**). Di-substituted isatins such as 4,7-dichloro isatin also reacted very smoothly to afford the desired product **3i** with complete γ-regioselectivity. The obtained regioselectivity of compound **3i** was also confirmed by single crystal X-ray data (Fig. 2; see also Supplementary Material for detailed single crystal X-ray data).

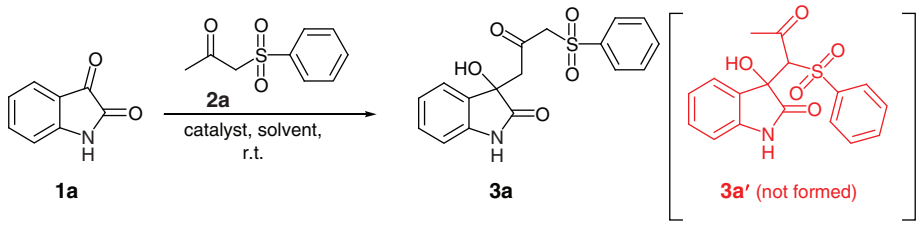
α-Substituted β-keto sulfones also reacted smoothly under standard reaction conditions and afford the desired γ-addition products in good yield as a mixture of inseparable diastereomers (Table 2, products **3k**–**p**). All the screed structurally varied β-keto sulfones underwent γ-addition on different isatins to provide γ-(3-hydroxy-2-oxindole)-β-keto sulfone structural scaffolds under mild reaction conditions.

The formation of γ-regioselective products can be explained on the basis of a previous study.[17a] When β-keto sulfones like 1-(phenylsulfonyl)propan-2-one are treated with DABCO, along with the major thermodynamic enolate product, a trace amount of kinetic enolate also might form because of the presence of an acidic proton at the γ-carbon atom (Scheme 5). Because of less steric interaction of the kinetic enolate with isatin, the nucleophilicity of the kinetic enolate might have increased and hence it reacts effectively with isatin to afford the γ-addition product **3a** exclusively (Path 2). Even though the kinetic enolate is present in trace amounts, its formation equilibrium is shifted forwards by its reaction with isatin and hence the reaction proceeds to completion to form a product.



Scheme 4. Reaction of isatin with 1-(phenylsulfonyl)propan-2-one using the dianion method (LDA: lithium diisopropylamine).

Table 1. Optimization of reaction conditions[A]

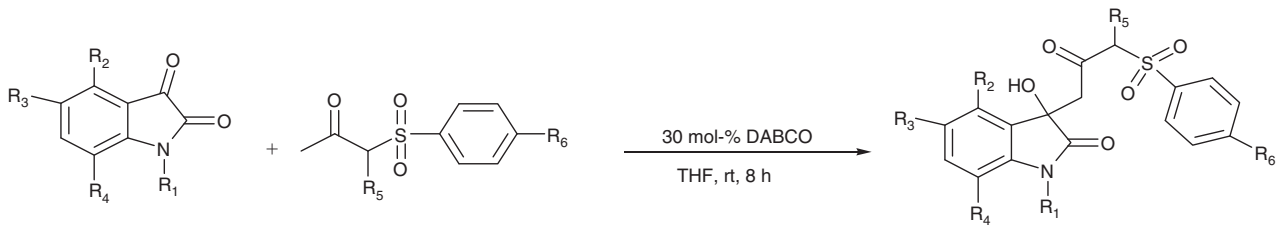


Entry	Solvent	Catalyst[B] (mol-%)	Time [h]	Yield[C] [%] **3a**/**3a′**
1	THF	DABCO (10)	24	91/00
2	THF	DABCO (10)	8	31/00
3	THF	DABCO (30)	8	90/00
4	THF	DABCO(100)	8	91/00
5	THF	TEA (30)	8	73/00
6	THF	DIPEA (30)	8	78/00
7	THF	DBU (30)	8	61/00
8	THF	DBN (30)	8	63/00
9	THF	Piperidine (30)	8	69/00
10	THF	Imidazole (30)	8	71/00
11	THF	DMAP (30)	8	64/00
12	MeCN	K_2CO_3 (30)	8	76/00
13	MeCN	Cs_2CO_3 (30)	8	71/00
14	MeOH	MeONa (30)	8	78/00
15	EtOH	EtONa (30)	8	71/00
16	THF	NaH (30)	8	58/00
17	THF	–	24	00/00

[A]Reaction conditions: isatin (1 mmol), 1-(phenylsulfonyl) propan-2-one (1 mmol) in 5 mL of solvent.
[B]DABCO: 1,4-diazabicyclo[2.2.2]octane, TEA: triethyamine, DIPEA: diisopropylethylamine, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DBN: 1,5-diazabicyclo[4.3.0]non-5-ene, DMAP: 4-dimethylaminopyridine.
[C]Determined by ^{1}H NMR analysis.

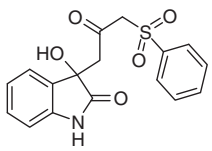
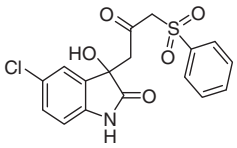
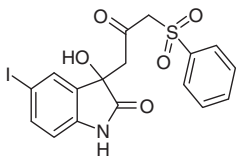
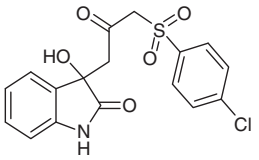
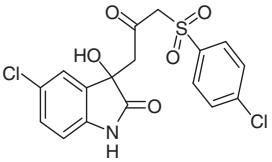
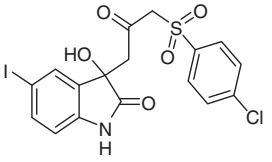
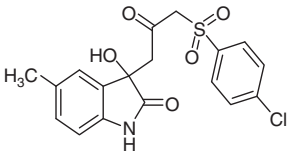
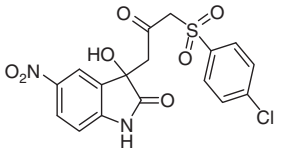
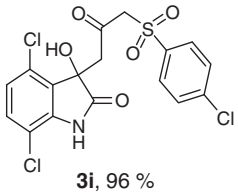
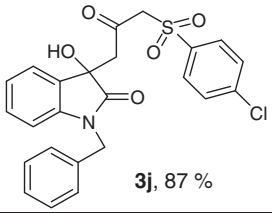
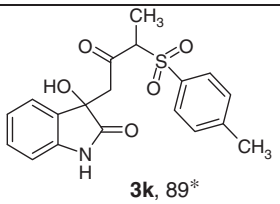
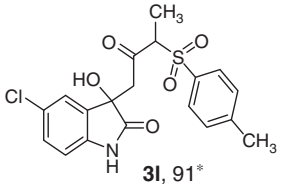
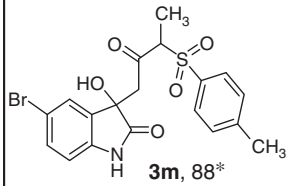
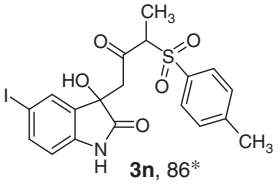
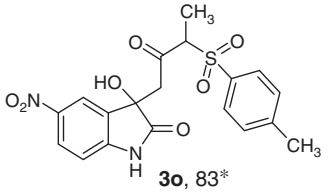
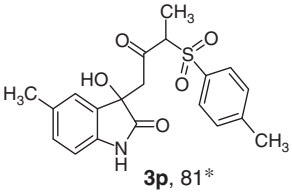
Table 2. The scope of the aldol reaction of β-keto sulfones with isatins under optimized reaction condition

Reaction conditions: isatin **1a**–**h** (1 mmol), β-keto sulfone **2a**–**c** (1 mmol) in 5 mL THF in the presence of 30 mol-% (DABCO). Yields are given as an isolated yield. * denotes an inseparable mixture of diasteromers, threo : erythro ratio written in parentheses



1a–h **2a–c** **3a–p**

R_1 = H, Bn; R_2 = H, Cl; R_3 = H, Cl, Br, I, NO_2, Me; R_4 = H, Cl; R_5 = H, Me; R_6 = H, Cl, Me

 **3a**, 88 %	 **3b**, 94 %	 **3c**, 84 %	 **3d**, 91 %
 **3e**, 92 %	 **3f**, 88 %	 **3g**, 81 %	 **3h**, 94 %
 **3i**, 96 %	 **3j**, 87 %	 **3k**, 89* dr, (57 : 43)	 **3l**, 91* dr, (56 : 44)
 **3m**, 88* dr, (55 : 45)	 **3n**, 86* dr, (59 : 41)	 **3o**, 83* dr, (59 : 41)	 **3p**, 81* dr, (63 : 37)

Conclusions

To conclude, we demonstrate the use of DABCO in the regioselective γ-addition of β-keto sulfones to isatins to afford diversely functionalized γ-(3-hydroxy-2-oxindole)-β-keto sulfone structural scaffolds under metal-free reaction conditions. The developed method provides straightforward access to a novel class of 3-substituted 3-hydroxy-2-oxindole frameworks in very good yields under mild reaction conditions from readily available starting materials. The method is applicable to a variety of functionalized isatins as well as β-keto sulfones. The attached β-keto sulfone framework on the 3-hydroxy-2-oxindole molecule provides an additional functional handle for further transformations which can be effectively utilized in natural product synthesis and the preparation of a library of pharmaceutically important compounds.

Experimental

Materials and Equipment

All ^{1}H and ^{13}C NMR spectra were recorded in d_6-DMSO on an Avance 300 MHz or Inova 500 MHz spectrometer, respectively.

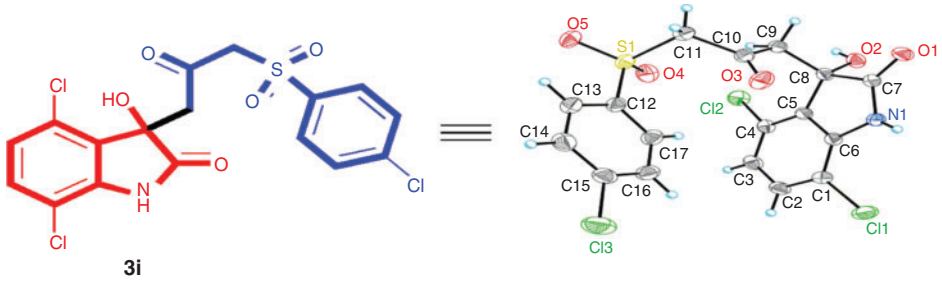
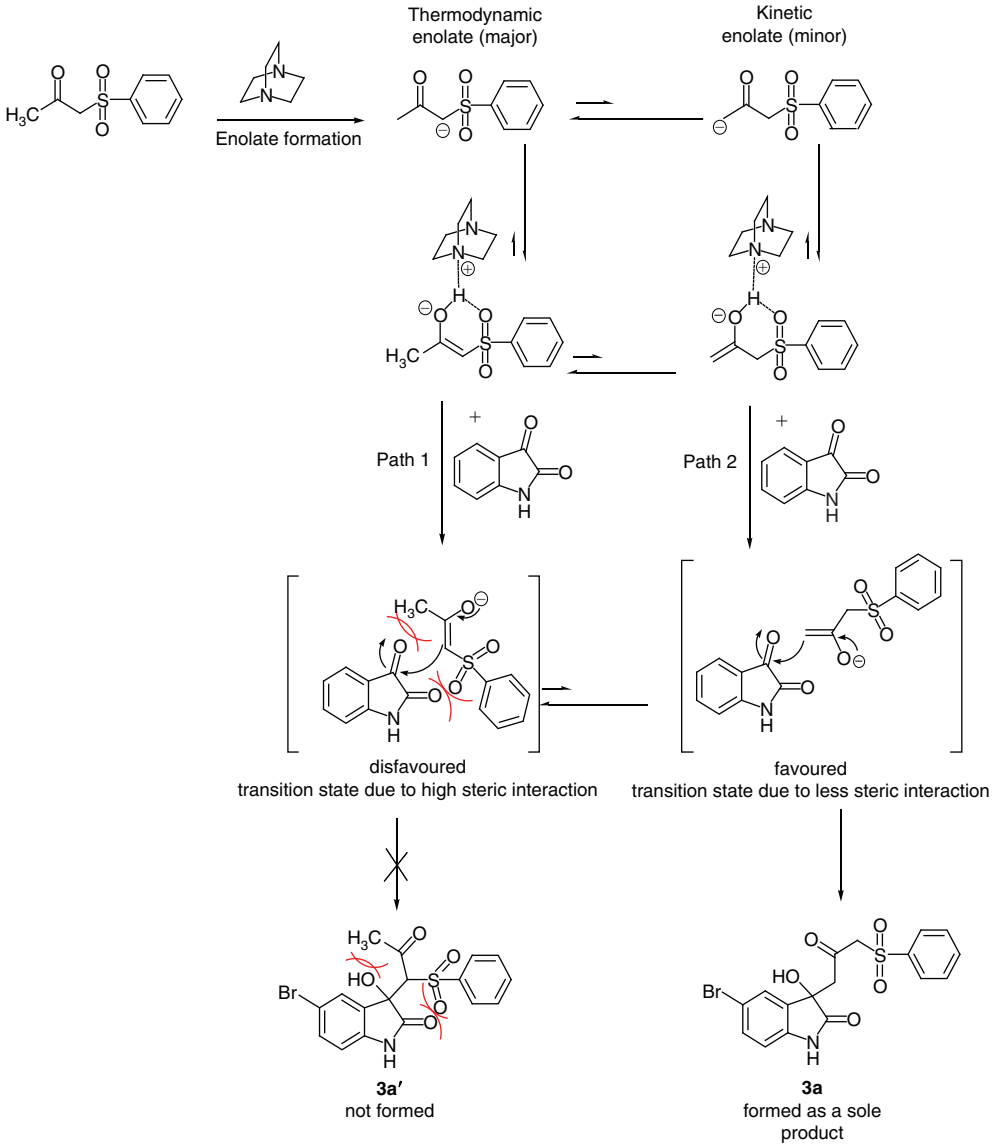


Fig. 2. Single crystal X-ray structure of compound **3i**.



Scheme 5. Plausible mechanism for the formation of γ-addition product in the aldol reaction of β-keto sulfone with isatins.

Chemical shifts (δ) are reported in parts per million (ppm) relative to either residual TMS (^{1}H: 0.00 ppm, ^{13}C: 00.00 ppm) or d_6-DMSO (^{1}H: 2.50 ppm, ^{13}C: 39.43 ppm) as an internal reference. Melting points were measured on a BUCHI melting point machine. IR spectra were recorded on Thermo Nicolet FT/IR-5700 spectrometer. Mass spectra were recorded using Waters mass spectrometers. High resolution mass spectrometry (HRMS) was performed using an Applied Bio-Sciences HRMS spectrometer.

Typical Experimental Procedure for the DABCO Catalyzed γ-Addition of β-Keto Sulfones to Isatins

To a stirred solution of β-keto sulfone (1.0 mmol) and DABCO (30 mol-%) in 5 mL of THF was added isatin (1 mmol). The

mixture was then stirred at room temperature for a stipulated time (Table 2). After completion of the reaction as indicated by TLC, the solvent was removed at reduced pressure on a BUCHI rotary evaporator. The residue was then purified by column chromatography on silica gel (hexane/ethyl acetate, 4 : 1–1 : 1) to afford the desired product. (See Supplementary Material for spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra for all synthesized compounds **3a**–**p**.)

Characterization Data

*3-Hydroxy-3-[2-oxo-3-(phenylsulfonyl)propyl]-1,3-dihydro-2H-indol-2-one (**3a**, Table 2)*

Yield 88 %, 0.303 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.10, pale yellow solid, mp 62–64°C. δ_H (300 MHz, $CDCl_3$ + d_6-DMSO) 10.09 (br s, 1H), 7.80–7.61 (m, 3H), 7.57–7.46 (m, 2H), 7.25–7.17 (m, 2H), 6.95 (t, *J* 7.6, 1H), 6.83 (d, *J* 7.6, 1H), 6.2 (br s, 1H), 4.55 (d, *J* 13.6, 1H), 4.32 (d, *J* 13.6, 1H) 3.45 (d, *J* 16.6, 1H), 3.21 (d, *J* 16.6, 1H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) 194.4, 177.2, 141.1, 137.42, 133.0, 129.5, 128.4, 128.1, 127.1, 123.0, 120.9, 109.2, 72.3, 65.7, 50.1. ν_{max} (KBr)/cm^{-1} 3329, 2927, 1723, 1622, 1473, 1317, 1153, 1081, 1032, 753, 687, 529. *m/z* (ESI) 368 $[M + Na]^+$. *m/z* 368.05582. HRMS Anal. Calc. for $C_{17}H_{15}O_5NSNa$ $[M + Na]^+$ 368.05631.

*5-Chloro-3-hydroxy-3-[2-oxo-3-(phenylsulfonyl) propyl]-1,3-dihydro-2H-indol-2-one (**3b**, Table 2)*

Yield 94 %, 0.356 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.25, white solid, mp 137–139°C. δ_H (200 MHz, $CDCl_3$ + d_6-DMSO) 10.22 (br s, 1H), 7.73 (d, *J* 7.4, 2H), 7.66 (t, *J* 7.4, 1H), 7.52 (t, *J* 7.7, 2H) 7.21 (d, *J* 1.7, 1H), 7.17 (dd, *J* 8.1, 1.7, 1H), 6.77 (d, *J* 8.3, 1H), 6.29 (br s, 1H), 4.52 (d, *J* 13.6, 1H), 4.32 (d, *J* 13.6, 1H), 3.50 (d, *J* 17.2, 1H), 3.26 (d, *J* 17.2, 1H). δ_C (50 MHz, $CDCl_3$ + d_6-DMSO) 194.1, 176.8, 139.90, 137.3, 132.8, 131.3, 127.9, 127.8, 126.8, 125.1, 123.1, 109.9, 71.8, 65.3, 49.7. ν_{max} (KBr)/cm^{-1} 3378, 3274, 2994, 2898, 1761, 1712, 1621, 1482, 1317, 1160, 1025, 882, 745, 528. *m/z* (ESI) 380 $[M + H]^+$. *m/z* 380.03611. HRMS Anal. Calc. for $C_{17}H_{15}ClNO_5S$ $[M + H]^+$ 380.03595.

*3-Hydroxy-5-iodo-3-[2-oxo-3-(phenylsulfonyl)propyl]-1,3-dihydro-2H-indol-2-one (**3c**, Table 2)*

Yield 84 %, 0.395 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.13, yellow solid, mp 102–104°C. δ_H (200 MHz, $CDCl_3$ + d_6-DMSO) 9.98 (br s, 1H), 7.94–7.78 (m, 1H), 7.58–7.48 (m, 6H), 7.45 (br s, 1H), 6.62 (d, *J* 8.1, 1H), 4.43 (d, *J* 13.4, 1H), 4.20 (d, *J* 13.3, 1H), 3.47 (d, *J* 16. 8, 1H), 3.25 (d, *J* 16.8, 1H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) 194.7, 177.0, 141.5, 137.6, 132.6, 132.2, 128.7, 128.6, 127.7, 112.0, 82.7, 72.7, 66.5, 50.5. ν_{max} (KBr)/cm^{-1} 3316, 2927, 2856, 1724, 1614, 1474, 1310, 1149, 1080, 731, 687, 527. *m/z* (ESI) 494 $[M + Na]^+$. *m/z* 493.95346. HRMS Anal. Calc. for $C_{17}H_{14}O_5NISNa$ $[M + Na]^+$ 493.95296.

*3-{3-[(4-Chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2H-indol-2-one (**3d**, Table 2)*

Yield 91 %, 0.345 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.13, pale yellow solid, mp 132–134°C. δ_H (500 MHz, $CDCl_3$ + d_6-DMSO) 9.78 (br s, 1H), 7.66 (d, *J* 8.5, 2H), 7.44 (d, *J* 8.5, 2H), 7.26 (d, *J* 7.4, 1H), 7.22 (t, *J* 7.4, 1H), 6.98 (t, *J* 7.4, 1H), 6.85 (d, *J* 7.4, 1H), 5.95 (br s, 1H), 4.53 (d, *J* 14.9, 1H), 4.31 (d, *J* 13.8, 1H) 3.41 (d, *J* 17.0, 1H), 3.22 (d, *J* 16.0, 1H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) 195.0, 177.8, 141.3, 139.9, 136.2, 129.7, 129.4, 129.0, 128.7, 123.5, 121.6, 109.8, 72.9, 66.1, 50.1. ν_{max} (KBr)/cm^{-1} 3359, 3093, 2927, 1723, 1621, 1579, 1475, 1394, 1324, 1154, 1086, 1034, 761, 654, 559, 467. *m/z* (ESI) 402 $[M + Na]^+$. *m/z* 402.01675. HRMS Anal. Calc. for $C_{17}H_{14}O_5N$-$ClSNa$ $[M + Na]^+$ 402.01734.

*5-Chloro-3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2H-indol-2-one (**3e**, Table 2)*

Yield 92 %, 0.380 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.22, white solid, mp 161–163°C. δ_H (300 MHz, $CDCl_3$ + d_6-DMSO) 10.24 (br s, 1H), 7.70 (d, *J* 9.1, 2H), 7.50 (d, *J* 8.3, 2H), 7.26–7.13 (m, 2H), 6.79 (d, *J* 8.30, 1H), 6.32 (br s, 1H), 4.56 (d, *J* 13.6, 1H), 4.39 (d, *J* 14.4, 1H), 3.48 (d, *J* 17.4, 1H), 3.26 (d, *J* 17.4, 1H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) 193.9, 175.7, 139.6, 137.9, 135.6, 131.0, 128.1, 127.4, 127.1, 124.0, 122.4, 109.2, 71.0, 64.1, 48.9. ν_{max} (KBr)/cm^{-1} 3429, 3236, 2898, 1714, 1621, 1475, 1393, 1328, 1153, 1089, 1037, 822, 767, 648, 553. *m/z* (ESI) 436 $[M + Na]^+$. *m/z* 435.97803. HRMS Anal. Calc. for $C_{17}H_{13}O_5NCl_2SNa$ $[M + Na]^+$ 435.97837.

*3-{3-[(4-Chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-5-iodo-1,3-dihydro-2H-indol-2-one (**3f**, Table 2)*

Yield 88 %, 0.444 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.30, brown solid, mp 67–69°C. δ_H (200 MHz, $CDCl_3$ + d_6-DMSO) 10.25 (br s, 1H), 7.69 (d, *J* 8.5, 2H), 7.61–7.42 (m, 4H), 6.65 (d, *J* 8.7, 1H), 6.29 (br s, 1H), 4.55 (d, *J* 14.0, 1H), 4.36 (d, *J* 14.0, 1H), 3.48 (d, *J* 17.18, 1H), 3.27 (d, *J* 17.2, 1H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) 194.1, 175.9, 141.0, 138.8, 136.4, 135.6, 132.0, 131.2, 128.6, 127.9, 110.9, 82.5, 71.4, 65.0, 49.5. ν_{max} (KBr)/cm^{-1} 3376, 3272, 2929, 1755, 1716, 1612, 1472, 1319, 1154, 1083, 1021, 818, 761, 642, 529, 464. *m/z* (ESI) 506 $[M + H]^+$. *m/z* 505.93336. HRMS Anal. Calc. for $C_{17}H_{14}ClI$-NO_5S $[M + H]^+$ 505.93259.

*3-{3-[(4-Chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-5-methyl-1,3-dihydro-2H-indol-2-one (**3g**, Table 2)*

Yield 81 %, 0.318 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.26, light orange solid, mp 65–67°C. δ_H (200 MHz, $CDCl_3$ + d_6-DMSO) 9.64 (br s, 1H), 7.65 (d, *J* 8.5, 2H) 7.44 (d, *J* 8.7, 2H), 7.07 (s, 1H), 7.03 (d, *J* 7.9, 1H), 6.74 (d, *J* 7.9, 1H), 5.90 (br s, 1H), 4.53 (d, *J* 13.8, 1H), 4.31 (d, *J* 13.8, 1H) 3.38 (d, *J* 16.1, 1H), 3.21 (d, *J* 16.1, 1H), 2.29 (s, 3H). δ_C (50 MHz, $CDCl_3$ + d_6-DMSO) 195.1, 177.9, 139.9, 138.7, 136.2, 131.1, 129.7, 129.4, 129.3, 128.8, 124.3, 109.6, 73.1, 66.1, 50.5, 20.4. ν_{max} (KBr)/cm^{-1} 3364, 2923, 1721, 1627, 1493, 1322, 1154, 1087, 1033, 821, 764, 559, 468. *m/z* (ESI) 416 $[M + Na]^+$. *m/z* 416.03421. HRMS Anal. Calc. for $C_{18}H_{16}ClNO_5SNa$ $[M + Na]^+$ 416.03354.

*3-{3-[(4-Chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-5-nitro-1,3-dihydro-2H-indol-2-one (**3h**, Table 2)*

Yield 94 %, 0.398 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.13, white solid, mp 176–178°C. δ_H (500 MHz, d_6-DMSO) 10.64 (br s, 1H), 8.20–8.12 (m, 2H), 7.71 (d, *J* 8.3, 2H), 7.48 (d, *J* 8.3, 2H), 6.95 (d, *J* 9.3, 1H), 6.36 (br s, 1H), 4.41 (d, *J* 13.5, 1H), 4.34 (d, *J* 14.5, 1H), 3.57 (d, *J* 17.6, 1H), 3.43 (d, *J* 17.6, 1H). δ_C (75 MHz, d_6-DMSO) 194.7, 177.7, 148.2, 142.1, 140.0, 136.2, 129.2, 128.8, 128.1, 125.9, 119.4, 109.4, 72.1, 65.9, 50.3. ν_{max} (KBr)/cm^{-1} 3359, 3128, 2927, 1717, 1623, 1522,

1471, 1334, 1161, 1094, 835, 795, 744. *m/z* (ESI) 447 $[M+Na]^+$. *m/z* 447.00258. HRMS Anal. Calc. for $C_{17}H_{13}ClN_2O_7SNa$ $[M+Na]^+$ 447.00242.

*4,7-Dichloro-3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3i**, Table 2)*

Yield 96 %, 0.429 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.33, white solid, mp 180–182°C. δ_H (500 MHz, $CDCl_3$ + d_6-DMSO) 10.35 (br s, 1H), 7.75 (d, *J* 7.2, 2H), 7.49 (d, *J* 7.2, 2H), 7.15 (d, *J* 9.6, 1H), 6.85 (d, *J* 7.2, 1H), 6.31 (br s, 1H), 4.46 (d, *J* 14.3, 1H), 4.35 (d, *J* 14.3, 1H), 3.74 (d, *J* 16.7, 1H), 3.58 (d, *J* 16.7, 1H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) 194.2, 175.8, 140.9, 138.9, 135.9, 129.2, 128.6, 128.0, 127.6, 127.0, 122.1, 112.3, 73.1, 64.8, 48.0. ν_{max} (KBr)/cm^{-1} 3484, 3218, 3089, 2925, 1731, 1612, 1470, 1322, 1156, 1089, 1032, 943, 765, 621, 562. *m/z* (ESI) 448 $[M+H]^+$. *m/z* 447.95776. HRMS Anal. Calc. for $C_{17}H_{13}O_5NCl_3S$ $[M+H]^+$ 447.95745.

*1-Benzyl-3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3j**, Table 2)*

Yield 87 %, 0.408 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.38, orange viscous liquid. δ_H (500 MHz, $CDCl_3$ + d_6-DMSO) 7.56 (d, *J* 7.1, 2H), 7.39–7.27 (m, 5H), 7.28–7.18 (m, 3H), 7.14 (t, *J* 7.1, 1H), 6.98 (t, *J* 7.1, 1H), 6.62 (d, *J* 7.1, 1H), 6.16 (br s, 1H), 4.70 (d, *J* 15.3, 1H), 4.76 (d, *J* 15.3, 1H), 4.44 (d, *J* 13.3, 1H), 4.27 (d, *J* 13.3, 1H), 3.58 (d, *J* 17.3, 1H), 3.42 (d, *J* 17.3, 1H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) 194.8, 176.0, 142.5, 139.9, 135.9, 135.0, 129.4, 129.3, 129.0, 128.7, 128.0, 126.9, 126.6, 123.3, 122.1, 108.9, 72.5, 66.1, 50.8, 43.1. ν_{max} (KBr)/cm^{-1} 3420, 2925, 2854, 1720, 1614, 1580, 1491, 1469, 1357, 1325, 1282, 1156, 1087, 1065, 761, 701, 564. *m/z* (ESI) 492 $[M+Na]^+$. *m/z* 492.06387. HRMS Anal. Calc. for $C_{24}H_{20}O_5NClSNa$ $[M+Na]^+$ 492.06429.

*3-Hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3k**, Table 2)*

Yield 89 %, 0.332 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.13, white solid, mp 171–173°C. δ_H (300 MHz, $CDCl_3$ + d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 57 : 43, * denotes minor diastereomer peaks) 9.85* (br s, 1H), 9.79 (br s, 1H), 7.71–7.51* (m, 4H), 7.49–7.38* (m, 2H), 7.36–7.24 (m, 4H), 7.20–7.15 (m, 2H), 7.04 (t, *J* 7.6, 1H), 6.97* (t, *J* 7.6, 1H), 6.89 (d, *J* 7.7, 1H), 6.85* (d, *J* 7.7, 1H), 5.95 (br s, 1H), 5.92* (br s, 1H), 4.50 (q, *J* 6.8, 1H), 4.38* (q, *J* 6.8, 1H), 3.73 (d, *J* 17.4, 1H), 3.65* (d, *J* 15.5, 1H), 3.47 (d, *J* 17.5, 1H), 3.18* (d, *J* 15.5, 1H), 2.43* (s, 3H), 2.40 (s, 3H), 1.27 (d, *J* 8.5, 3H), 1.23* (d, *J* 6.8, 3H). δ_C (75 MHz, d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 57 : 43, * denotes minor diastereomer peaks) 198.1*, 198.0, 177.2, 177.1*, 144.0*, 143.8, 141.4, 141.0*, 132.0, 131.1, 131.0*, 129.9*, 129.7, 129.3*, 128.4*, 128.2, 128.1, 127.9*, 127.4, 122.9*, 122.9, 120.6*, 120.5, 108.9*, 108.9, 72.5*, 72.0, 69.0*, 67.6, 50.5, 49.5* 20.3*, 20.3, 10.4, 10.0*. ν_{max} (KBr)/cm^{-1} 3475, 3415, 3205, 2922, 1715, 1623, 1475, 1298, 1144, 1074, 749, 715, 656, 573. *m/z* (ESI) 396 $[M+Na]^+$. *m/z* 396.08691. HRMS Anal. Calc. for $C_{19}H_{19}O_5NSNa$ $[M+Na]^+$ 396.08761.

*5-Chloro-3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3l**, Table 2)*

Yield 91 %, 0.370 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.29, white solid, mp 85–87°C. δ_H (500 MHz, $CDCl_3$ + d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 56 : 44, * denotes minor diastereomer peaks) 9.91* (br s, 1H), 9.87 (br s, 1H), 7.60–7.53* (m, 3H), 7.42–7.36 (m, 3H), 7.30* (d, *J* 8.7, 2H), 7.25 (dd, *J* 8.7, 1.7, 1H), 7.22 (d, *J* 7.8, 2H), 7.17* (dd, *J* 8.7, 2.3, 1H), 6.82 (d, *J* 8.7, 1H), 6.79* (d, *J* 8.7, 1H), 6.00 (br s, 1H), 5.94* (br s, 1H), 4.45 (q, *J* 7.0, 1H), 4.35* (q, *J* 7.0, 1H), 3.70 (d, *J* 17.4, 1H), 3.62* (d, *J* 16.5, 1H), 3.46 (d, *J* 17.4, 1H), 3.27* (d, *J* 16.5, 1H), 2.43* (s, 3H), 2.41 (s, 3H), 1.26* (d, *J* 6.9, 3H), 1.25 (d, *J* 6.9, 3H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 56 : 44, * denotes minor diastereomer peaks) 197.9*, 197.7, 176.6*, 176.5, 143.9*, 143.9, 140.3, 139.9*, 131.7*, 131.5, 131.3*, 131.1, 129.8, 128.3*, 128.2, 128.0, 127.9*, 127.7*, 127.7, 127.4, 125.0, 123.3*, 123.1, 109.9, 72.2*, 71.8, 68.7*, 67.5, 50.3, 49.0*, 20.3*, 20.3, 10.3, 10.0*. ν_{max} (KBr)/cm^{-1} 3327, 2925, 2859, 1727, 1622, 1477, 1311, 1143, 1077, 1010, 817, 722, 653, 580. *m/z* (ESI) 408 $[M+H]^+$. *m/z* 408.06650. HRMS Anal. Calc. for $C_{19}H_{19}O_5NClS$ $[M+H]^+$ 408.06670.

*5-Bromo-3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3m**, Table 2)*

Yield 88 %, 0.417 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.19, brown solid, mp 170–172°C. δ_H (500 MHz, $CDCl_3$ + d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 55 : 45, * denotes minor diastereomer peaks) 10.92* (br s, 1H), 10.67 (br s, 1H), 7.72–7.66* (m, 3H), 7.43–7.37 (m, 3H), 7.29* (d, *J* 8.6, 2H), 7.26 (dd, *J* 8.6, 1.7, 1H), 7.24 (d, *J* 8.1, 2H), 7.18* (dd, *J* 8.6, 2.3, 1H), 6.73 (d, *J* 8.7, 1H), 6.69* (d, *J*,8.7, 1H), 6.01 (br s, 1H), 5.95* (br s, 1H), 4.46 (q, *J* 7.0, 1H), 4.34* (q, *J* 7, 1H), 3.71 (d, *J* 17.4, 1H), 3.63* (d, *J* 16.5, 1H), 3.47 (d, *J* 17.4, 1H), 3.27* (d, *J* 16.5, 1H), 2.43* (s, 3H), 2.41 (s, 3H), 1.27* (d, *J* 6.9, 3H), 1.25 (d, *J* 6.9, 3H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 55 : 45, * denotes minor diastereomer peaks) 198.27, 198.05*, 176.81*, 176.88, 144.50*, 144.25, 140.81*, 140.44, 132.06*, 131.85, 131.05, 130.71*, 128.90*, 128.66, 128.47*, 128.38, 128.09, 128.01*, 126.32, 126.15*, 124.82*, 124.32, 123.13, 112.98*, 110.88, 72.54, 72.11*, 69.45, 68.90*, 50.48*, 49.19* 20.05, 19.96*, 10.53*, 10.24. ν_{max} (KBr)/cm^{-1} 3383, 3245, 2925, 1748, 1619, 1480, 1304, 1142, 1068, 1009, 830, 720, 650, 581. *m/z* (ESI) 474 $[M+Na]^+$. *m/z* 473.99929. HRMS Anal. Calc. for $C_{19}H_{18}BrNO_5SNa$ $[M+Na]^+$ 473.99868.

*3-Hydroxy-5-iodo-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3n**, Table 2)*

Yield 86 %, 0.429 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.31, Yellow solid, mp 216–218°C. δ_H (200 MHz, d_6-DMSO) (inseparable diastereomeric ratio, *major : minor*, 59 : 41, * denotes minor diastereomer peaks) 10.06* (br s, 1H), 10.04 (br s, 1H), 7.68* (d, *J* 1.0, 2H), 7.59–7.50 (m, 4H), 7.39–7.28* (m, 4H), 7.23 (d, *J* 8.1, 2H), 6.68 (d, *J* 8.3, 1H), 6.65* (d, *J* 8.3, 1H), 6.15 (br s, 1H), 6.10* (br s, 1H), 4.50–4.43 (m, 1H), 4.37–4.30* (m, 1H), 3.73 (d, *J* 17.5, 1H), 3.63* (d, *J* 16.6, 1H), 3.44 (d, *J* 17.5, 1H), 3.27* (d, *J* 16.6, 1H), 2.44* (s, 3H), 2.42 (s, 3H), 1.34* (d, *J* 6.8, 3H), 1.24 (d, *J* 6.8, 3H). δ_C (50 MHz, d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 59 : 41, * denotes minor diastereomer peaks) 199.1*, 199.1, 177.0*, 176.9, 144.9, 142.5, 142.3*, 137.5, 133.7, 133.6*, 132.9, 132.2, 129.6*, 129.4, 128.9, 128.9*, 112.0, 119.9*, 83.9*, 83.8, 72.5*, 72.1, 68.8*, 67.9, 51.1, 50.1* 21.1, 11.2, 10.9*. ν_{max} (KBr)/cm^{-1} 3382, 3236, 2988, 1740, 1615, 1477, 1387, 1305, 1212, 1140, 1066, 1005, 828, 716, 646, 578. *m/z* (ESI) 517 $[M+NH_4]^+$. *m/z* 517.02999. HRMS Anal. Calc. for $C_{19}H_{22}IN_2O_5S$ $[M+NH_4]^+$ 517.02941.

*3-Hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-5-nitro-1,3-dihydro-2H-indol-2-one (**3o**, Table 2)*

Yield 83 %, 0.347 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.30, pale yellow solid, mp 199–201°C. δ_H (500 MHz, $CDCl_3$ + d_6-DMSO) (inseparable diastereomeric ratio, *major : minor*, 59 : 41, * denotes minor diastereomer peaks) 10.65 (br s, 1H), 10.64* (br s, 1H), 8.29–8.21* (m 2H), 8.20–8.13 (m, 2H), 7.57* (d, *J* 7.8, 2H), 7.4 (d, *J* 7.8, 2H), 7.30* (d, *J* 7.8, 2H), 7.21 (d, *J* 7.8, 2H), 6.99 (d, *J* 8.8, 1H), 6.97* (d, *J* 8.8, 1H), 6.34 (br s, 1H), 6.30* (br s, 1H), 4.49–4.39 (m, 1H), 4.38–4.31* (m, 1H), 3.80 (d, *J* 18.5, 1H), 3.73* (d, *J* 16.5, 1H), 3.54 (d, *J* 17.5, 1H), 3.52* (d, *J* 17.5, 1H), 2.43* (s, 3H), 2.41 (s, 3H) 1.32* (d, *J* 6.8, 3H), 1.26 (d, *J* 6.8, 3H). δ_C (50 MHz, $CDCl_3$ + d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 59 : 41, * denotes minor diastereomer peaks) 197.9*, 197.8, 176.9*, 176.8, 147.9, 147.8*, 143.8, 143.8*, 140.9*, 140.9, 131.5*, 131.3, 130.5, 130.4*, 128.2*, 128.0, 127.6*, 127.5, 124.9, 118.5, 108.4, 108.4*, 71.2*, 71.0, 68.1*, 67.2, 49.9, 49.0*, 20.0*, 20.0, 10.0, 9.9*. ν_{max} (KBr)/cm^{-1} 3289, 2931, 1715, 1624, 1520, 1456, 1327, 1141, 1006, 909, 715, 640. *m/z* (ESI) 441 $[M + Na]^+$. *m/z* 441.07398. HRMS Anal. Calc. for $C_{19}H_{18}N_2O_7SNa$ $[M + Na]^+$ 441.07324.

*3-Hydroxy-5-methyl-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2H-indol-2-one (**3p**, Table 2)*

Yield 81 %, 0.313 g, time 8 h, R_f (50 % EtOAc/hexanes) 0.19, brown solid, mp 80–82°C. δ_H (300 MHz, $CDCl_3$ + d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 63 : 37, * denotes minor diastereomer peaks) 9.72* (br s, 1H), 9.67 (br s, 1H), 7.53–7.41* (m, 3H), 7.27–7.18 (m, 3H), 7.15 (d, *J* 7.6, 1H), 7.10 (d, *J* 8.1, 2H), 6.98* (d, *J* 6.8, 2H), 6.92* (d, *J* 7.6, 1H), 6.68 (d, *J* 7.9, 1H), 6.64* (d, *J* 7.9, 1H), 5.90 (br s, 1H), 5.84* (br s, 1H), 4.45 (q, *J* 6.8 1H), 4.32* (q, *J* 6.8 1H), 3.58* (d, *J* 15.5, 1H), 3.53 (d, *J* 17.2, 1H), 3.37 (d, *J* 17.2, 1H), 3.05* (d, *J* 15.5, 1H), 2.08 (s, 3H), 2.08* (s, 3H), 2.08 (s, 3H), 2.08* (s, 3H) 1.19* (d, *J* 6.9, 3H), 1.14 (d, *J* 6.9, 3H). δ_C (75 MHz, $CDCl_3$ + d_6-DMSO) (inseparable diastereomeric ratio, major : minor, 63 : 37, * denotes minor diastereomer peaks) 198.71*, 198.41, 177.84, 177.70*, 144.71*, 144.26, 139.03, 138.57*, 132.28*, 131.37, 130.46, 130.20*, 129.91, 129.57*, 128.97*, 128.82, 128.54, 128.33*, 124.01, 109.26, 73.22*, 72.70, 69.58*, 68.12, 50.87, 49.75*, 22.02*, 21.72*, 20.73, 20.19, 10.81, 10.42*. ν_{max} (KBr)/cm^{-1} 3331, 2924, 1721, 1628, 1494, 1318, 1146, 1082, 817, 718, 656. *m/z* (ESI) 410 $[M + Na]^+$. *m/z* 410.10248. HRMS Anal. Calc. for $C_{20}H_{21}O_5NSNa$ $[M + Na]^+$ 410.10326.

*X-Ray Crystallographic Data for Compound 4,7-Dichloro-3-(3-(4-chlorophenylsulfonyl)-2-oxopropyl)-3-hydroxyindolin-2-one (**3i**, Table 2)*

Compound **3i,** $C_{17}H_{12}NO_5Cl_3S$, *M* 448.69, crystallized as colourless long needles. One crystal was selected and was cut before mounting on the goniometer. The diffraction data were collected on a crystal of 0.41 × 0.33 × 0.17 mm^3 size, monoclinic, space group $P2_1/c$ (No. 14), *a* 12.3354(11), *b* 8.2343(8), *c* 18.3236 (17) Å, β 104.167(2)°, *V* 1804.6(3) $Å^3$, *Z* 4, D_c 1.651 g cm^{-3}, F_{000} 912, CCD area detector, $Mo_{K\alpha}$ radiation, λ 0.71073 Å, *T* 294(2) K, $2\theta_{max}$ 50.0°, 14142 reflections collected, 3170 unique (R_{int} 0.0197). Final GoF 1.038, R_1 0.0280, wR_2 0.0766, *R* indices based on 2958 reflections with $I > 2\sigma(I)$ (refinement on F^2), 252 parameters, μ 0.654 mm^{-1}. CCDC 916506 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk)

Supplementary Material

Details of experimental procedures, characterisation data of products and copies of ^1H and ^{13}C NMR spectra are available on the Journal's website.

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