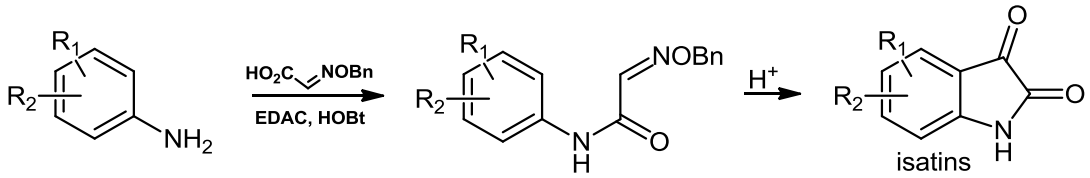
Larry L. Klein* and Michael D. Tufano

Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, 833 S. Wood Street, Chicago, Illinois-60612.

*Larry L. Klein
Research Professor
Institute for Tuberculosis Research
College of Pharmacy
University of Illinois at Chicago
833 S. Wood Street
Chicago, IL 60612
Ph: 312-413-9440
e-mail: llk@uic.edu
fax: 312-355-5539

Abstract:



Isatins are valuable intermediates for heterocyclic chemistry. Most of the common methods for their production are less than adequate when the number and lipophilicity of substituents on the targeted isatin are increased. Our group desired such molecules and identified an alternative method for their production.

Keywords: isatin; Sandmeyer isatin synthesis; oximinoacetanilides

Isatins (1H-indole-2,3-diones, **1**) are valuable intermediates in the field of heterocyclic and pharmaceutical chemistry [1]. Several of these derivatives show activities of biological interest [2] but most serve as templates in the construction of pharmaceutically active agents. Recently, we required multiply substituted isatins as intermediates and found the standard methods for their preparation to be less than optimal on a gram scale [3].

The most common procedure for the synthesis of isatins is the Sandmeyer process [4] which utilizes a mixture of chloral hydrate, an aniline (or its hydrochloride salt), hydroxylamine, and hydrochloric acid in a heated sodium sulfate-saturated aqueous media (Figure 1). The molecular mechanism for this process is believed to proceed through an initial glyoxamide **4** which reacts, in turn, with hydroxylamine to form the

oximinoacetanilide, **5** [5a,b]. Heating compound **5** to 90 °C in sulfuric acid affects the ring cyclization to produce the isatin, **1**.

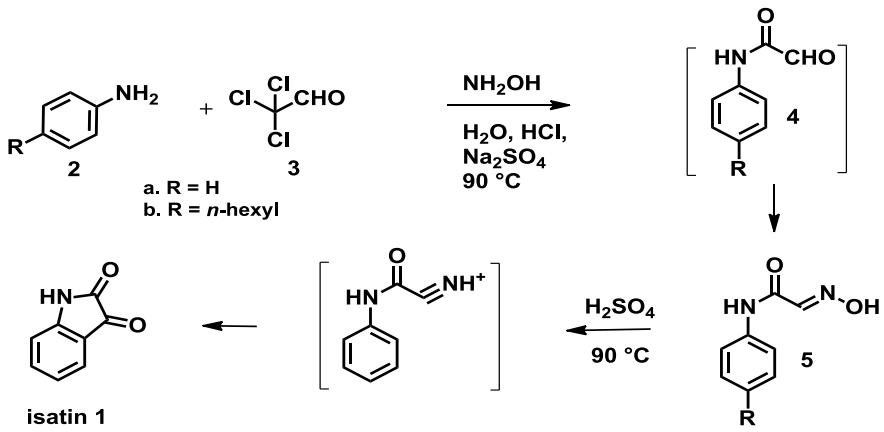


Figure 1. Sandmeyer isatin process

Although this process has worked for simple analogs (Figure 1, **2a**), as the substitution of the precursor anilines increases both in number and lipophilicity, the facility of this classical reaction to form the oximinoacetanilide intermediate **5** suffers. For example, when 4-*n*-hexylaniline (**2b**) was used as starting material, <5% yield of intermediate **5b** could be isolated. Attempts to modify this process through the use of co-solvents such as ethanol [6a] or microwave heating [6b] have helped obtain some products not otherwise available, albeit in moderate yields. The fact that the key reagent, chloral hydrate, is a regulated substance also impacts the potential to perform large scale production of the isatins.

An alternative method for production of intermediate **5** or its equivalent was envisioned involving a coupling reaction of an alkyloximinoacetic acid **6** (Figure 2) and an aniline under standard amide-forming conditions; however, though hydroxyiminoacetic acid (**6a**) is known [7], reaction of this compound with anilines failed to provide product **5**. Crystalline benzyloximinoacetic acid (**6b**) is available in multi-gram quantities via an extractive work-up following combination of *O*-benzylhydroxylamine and glyoxylic acid hydrate [8]. Coupling of **6b** to a variety of

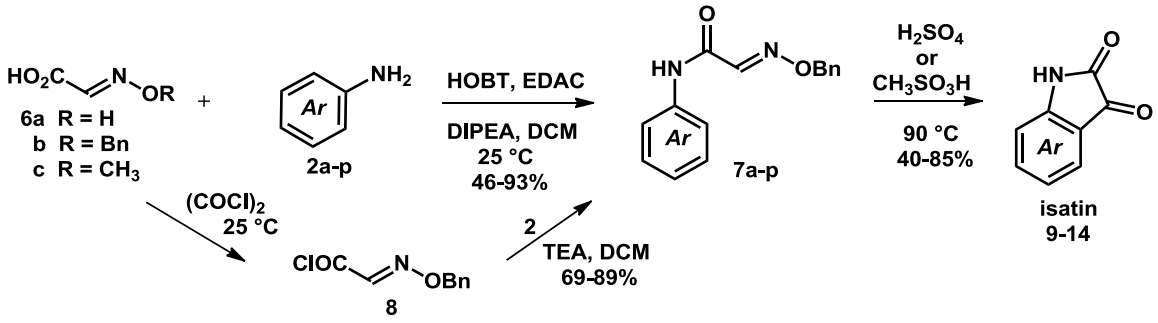


Figure 2. Synthesis of alkyloximinoacetanilides **7**.

substituted anilines led to good yields of the benzyoximinoacetanilides, **7** as shown in Table 1. The corresponding benzyloximinoacetyl chloride (**8**) is also available via treatment of **6b** with oxalyl chloride and serves equally well to produce substituted anilines **7** in the presence of bases such as triethylamine or diisopropylethylamine in common organic solvents (e.g. dichloromethane, tetrahydrofuran).

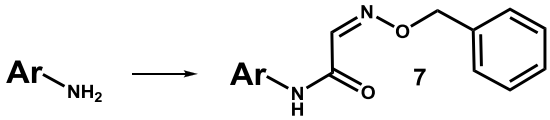


Table 1. Preparation of benzyloximinoacetanilides.

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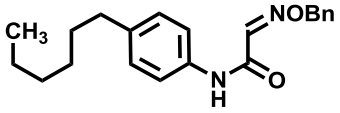
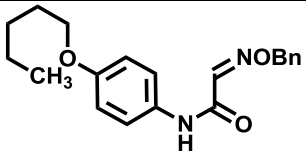
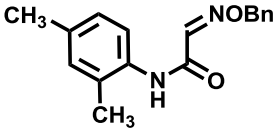
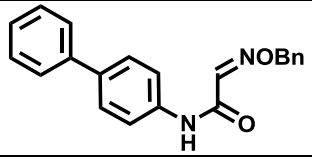
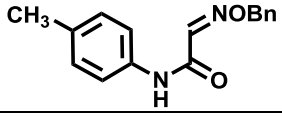
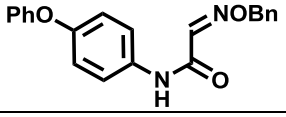
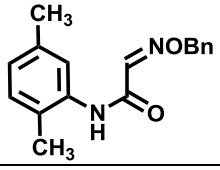
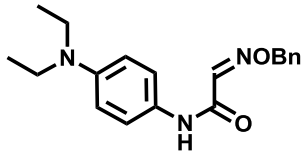
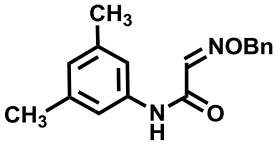
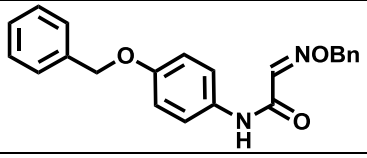
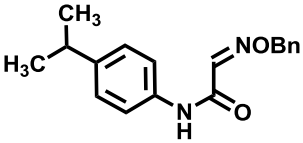
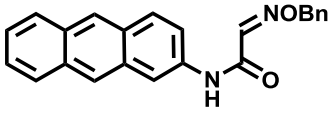
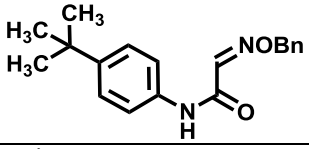
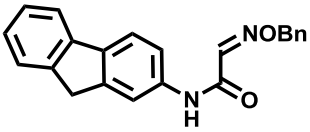
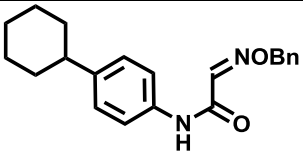
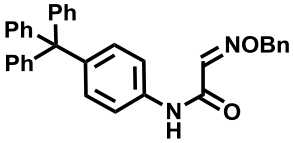
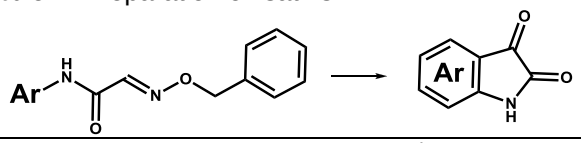
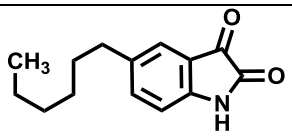
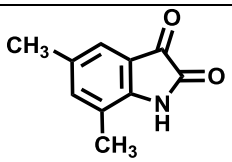
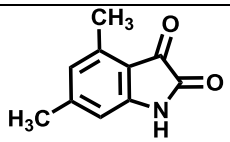
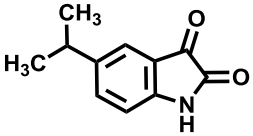
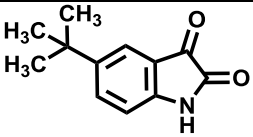
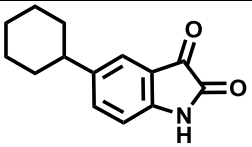
1		**7a**	A	85	9		**7i**	B	80
2		**7b**	B	75	10		**7j**	A	46
3		**7c**	B	69	11		**7k**	A	60
4		**7d**	A	79	12		**7l**	B	79
5		**7e**	B	87	13		**7m**	B	89
6		**7f**	A	93	14		**7n**	B	61
7		**7g**	B	88	15		**7o**	B	71
8		**7h**	B	89	16		**7p**	B	87

[a] Method A: $ArNH_2$, 1 eq. $HO_2CCH{=}NOBn$, 1.5 eq. EDAC, 1.5 eq. HOBt, 3 eq. DIPEA, THF, RT;
or Method B: $ArNH_2$, 1.05 eq. $ClCOCH{=}NOBn$, 1.15 eq. TEA, DCM, RT.

It has been suggested that the ring cyclization step in the Sandmeyer process involves a dehydration of the oxime to form the □-acylnitrile (Figure 1). In the case of the benzyl analog, rather than loss of water, the loss of benzyl alcohol would have to take place to form this same reactive intermediate. When **7a** was treated in this manner, the isatin product was formed in a similar yield as for the unsubstituted oximinoacetanilide, **5**. Since no chemical trace of the benzyl residue was apparent from this modified reaction, it is presumed that any such alkyl moiety can be used in this approach. This reaction sequence was carried out at a ten gram scale without change in the yield of isatin **9** produced (Table 2, entry 1).

Table 2. Preparation of isatins.



Entry	Product	Cpd #	Method[a]	Yield %
1		**9**	H_2SO_4	85
2		**10**	H_2SO_4	60
3		**11**	H_2SO_4	46
4		**12**	CH_3SO_3H	40
5		**13**	CH_3SO_3H	64
6		**14**	CH_3SO_3H	60

[a] Method A: H_2SO_4 at 50 °C, heat to 80 °C; add to ice; Method B: CH_3SO_3H at 50 °C, heat to 80 °C; add to ice.

When oximinoacetanilide analogs of high lipophilicity (eg. **7f-h**) were heated in sulfuric acid as per the classical Sandmeyer route, cyclization was frequently incomplete due to

the poor solubility under these conditions. Use of methanesulfonic acid [9] as the media with these three oximinoacetanilides proved to be helpful in circumventing the problems and served to provide the corresponding isatin products even when little or no product was available from the sulfuric acid method (Table 2). In general, yields of isatins were similar or slightly improved when methanesulfonic acid was used as the media.

In the case of the extremely insoluble aryl-containing examples such as **7p**, although heating in methanesulfonic acid produced isatins, uncharacterized impurities arising from the process were difficult to remove. The preparation of 5-tritylisatin (**16**) from 4-tritylaniline was chosen as the most difficult example for method modification. In order to further increase solubility in the acidic media and avoid these impurities, two modifications were employed: 1) the corresponding methyloximinoacetanilide, **15**, was utilized which was, in turn, prepared from acid **6c** [10](Figure 3), and 2) polyphosphoric acid (PPA) was used as the media. In this way, 5-tritylisatin (**16**) was produced in 67% yield.

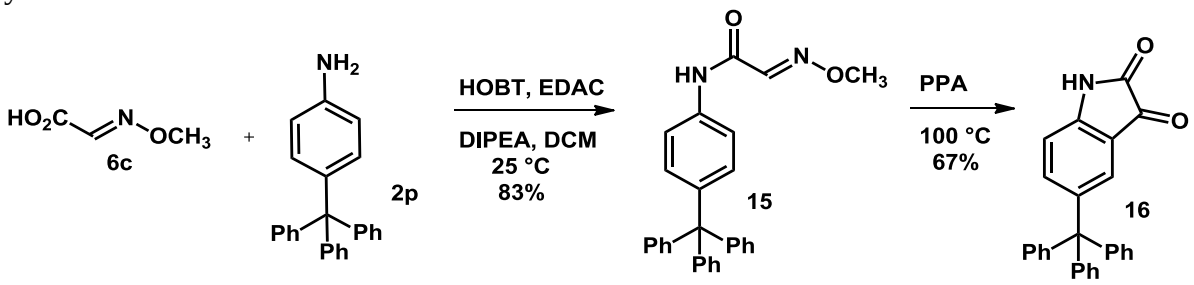


Figure 3. Synthesis of 5-tritylisatin (**16**).

The straightforward preparation of benzyl-, or in certain cases methyloximinoacetanilides (such as **7a-p,15**) and the heating of these intermediates in sulfuric acid, methanesulfonic acid, or, for poorly soluble analogs PPA, has been shown to afford substituted isatins. This modified aniline-to-isatin route circumvents many of the problems present in the classical Sandmeyer isatin synthesis and allows production of these substituted isatins in a reproducible manner.

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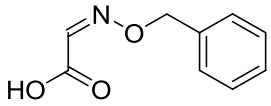
Supporting Information

EXPERIMENTAL

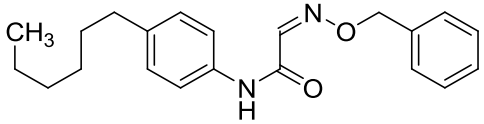
General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker spectrometers at 400MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS, 0.00 ppm) or calibrated on standard *d*-solvent signals (*d*6-DMSO, 39.52 ppm; $CDCl_3$, 77.16 ppm). HRMS were run on the Shimadzu LCMS-ITTOF ionization (ESI) mode. Chromatographic purifications were performed using pre-packed FLASH silica cartridges from Biotage or an HPFC Biotage SP1 system using prefilled KP-Sil (normal phase) SNAP cartridges with UV detection at 256 nm and 254 nm utilizing hexane/ethyl acetate gradients. Solvents were used as purchased from Fisher or in Sure-Seal bottles from Sigma-Aldrich. CEM Explorer 48/72/96 automated microwave synthesizer was used for microwave heated reactions (sealed) controlled by an external computer loaded with the Synergy application software (Version 1.1). DCM = dichloromethane, EtOAc = ethyl acetate, MeOH = methanol, THF = tetrahydrofuran, Hex = hexanes, DMF = dimethylformamide.

General Procedure for the synthesis of the oximinoacetanilides (7a-z)
METHOD A:



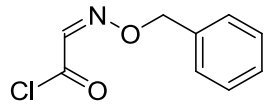
i. **2-[(Benzyloxy)imino]acetic acid (6b)**
The literature procedure[8] was followed using O-benzylhydroxylamine hydrochloride (10 g) to produce the product (10.76 g) as a crystalline compound in 96% yield.
^{1}H NMR ($CDCl_3$) δ ppm 5.31 (s, 2H), 7.4 (br.s, 5H), 7.54 (s, 1H); (-CO_2H proton not seen). ^{13}C NMR ($CDCl_3$) δ ppm 78.23, 128.22, 128.28, 128.31, 135.13, 139.76, 164.60.



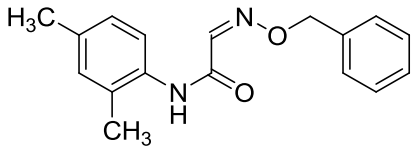
2-[(Benzyloxy)imino]-N-(4-hexylphenyl)acetamide (7a)
A solution of acid **6b** (2 g, 11.16 mmol), hydroxybenzotriazole (2.26 g, 16.74 mmol, 1.5 eq.), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC) (3.21 g, 16.74 mmol, 1.5 eq.) in THF/DMF (20/5ml) was stirred under nitrogen at 25 ^{o}C for 10 min. 4-*n*-Hexylaniline (1.98 g, 2.15 ml, 11.16 mmol, 1 eq.) and diisopropylethylamine (4.33 g, 33.5 mmol, 5.83 ml, 3 eq.) were added simultaneously dropwise to the reaction mixture.
After 2 h TLC analysis (10% EtOAc/Hex) showed complete reaction. The reaction was quenched with saturated ammonium chloride and EtOAc. The organic layer was separated, washed with water, brine, dried over sodium sulfate, and the solvents were evaporated. The crystallizing solids were triturated in petroleum ether (10 ml), filtered, and the solid (2.94 g) was rinsed with pet ether (15 ml). The mother liquor was treated again with pet ether to obtain 0.28 g more solid which was collected, the solids were combined, and vacuum dried to give a total of 3.22 g (85%) white solid.

^{1}H NMR ($CDCl_3$) δ ppm 0.87 (t, 3H), 1.29 (m, 6H), 1.58 (t, 2H), 2.57 (t, 2H), 5.26 (s, 2H), 7.15 (d, 2H), 7.39 (m, 5H), 7.47 (d, 2H), 7.55 (s, 1H), 8.15 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 14.06, 22.58, 28.87, 31.41, 31.69, 35.37, 77.66, 119.86, 128.32, 128.49, 128.63, 128.94, 134.55, 136.14, 139.47, 143.87, 159.19. HRMS [ESI] calculated for $C_{21}H_{26}N_2O_2$ ($M+H^+$) 339.2069; found 339.2067.

METHOD B:



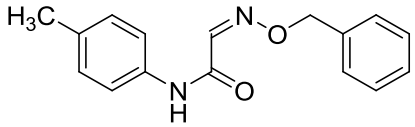
i. **2-[(Benzyloxy)imino]-acetyl chloride (8)**
To a solution of 2-[(benzyloxy)imino]acetic acid (0.815 g, 4.55 mmole) in DCM (30 ml) containing a catalytic amount of DMF (1 drop) was added oxalyl chloride (0.48 ml, 5.50 mmole, 1.2 eq.) dropwise at room temperature under nitrogen. On completion of the addition, the mixture was allowed to stir for 1 h. The solvents were evaporated at 30-35 ^{o}C and placed under high vacuum at room temperature to removed residual oxalyl chloride.



ii. **2-[(Benzyloxy)imino]-N-(2,4-dimethylphenyl)acetamide (7b)**

2-[(Benzyloxy)imino]acetyl chloride (**8**) (0.89 g, 4.55 mmole) was dissolved in DCM (20 ml) and added dropwise to an ice bath cooled solution of the 2,4-dimethylaniline (0.524 g, 4.32 mmole, 0.54 ml, 0.95 eq.) in DCM (30 ml) and N,N-diisopropylethylamine (0.95ml, 5.5 mmole, 1.2 eq.). On completion of the addition, the cold bath was removed, and the reaction mixture was allowed to warm to room temperature. The crude product was partitioned between 1% HCl and DCM. The organic phase was separated, washed with brine, dried over Na_2SO_4, and the solvents were evaporated. The resulting tan solid was triturated with 10% ether in hexane, filtered, rinsed with cold solvent mixture, and dried under vacuum to yield 0.96 g (3.40 mmole, 75%) of the title compound as an off-white solid.

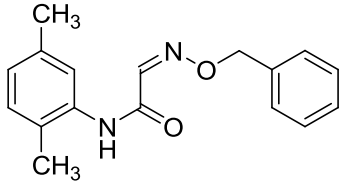
^{1}H NMR ($CDCl_3$) δ ppm 2.25 (s, 3H), 2.30 (s, 3H), 5.26 (s, 2H), 7.00-7.07 (m, 2H), 7.33-7.46 (cm, 5H), 7.78 (s, 1H), 7.81 (d,1H, J=7.85Hz), 8.12 (br.s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 17.05, 20.49, 77.34, 99.59, 121.85, 127.00, 128.11, 128.17, 128.24, 130.77, 131.95, 134.48, 135.77, 143.45, 158.91. HRMS [ESI] calculated for $C_{17}H_{18}N_2O_2$ ($M+H^+$) 283.1441; found 283.1445.



ii. **2-[(Benzyloxy)imino]-N-(4-methylphenyl)acetamide (7c)**

Following the procedure for **7b** (Method B), compound **7c** was produced in 69% yield.

^{1}H ($CDCl_3$) δ ppm 2.35 (s, 3H), 5.28 (s, 2H), 7.15 (d, 2H, J=8.2Hz), 7.30-7.60 (cm, 7H), 7.58 (s, 1H), 8.15 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 20.52, 77.29, 119.51, 127.95, 128.13, 128.27, 129.20, 133.94, 134.04, 135.77, 143.49, 158.83. HRMS [ESI] calculated for $C_{16}H_{16}N_2O_2$ ($M+H^+$) 269.1285; found 269.1294.

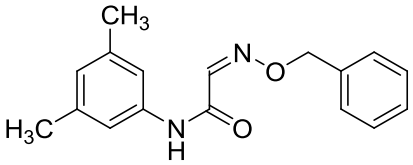


2-[(Benzyloxy)imino]-N-(2,5-dimethylphenyl)acetamide (7d)

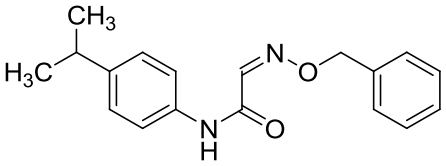
Following the procedure for **7a** (Method A), compound **7d** was produced in 79% yield.

^{1}H NMR ($CDCl_3$) δ ppm 2.23 (s, 3H), 2.34 (s, 3H), 5.26 (s, 2H), 6.9 (d, 1H, J=7.65Hz), 7.08, (d, 1H, J=7.65Hz), 7.32-7.45 (m, 5H), 7.57 (s, 1H), 7.83 (s, 1H), 8.16 (br.s, 1H).

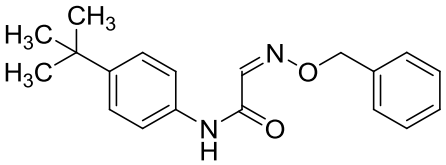
^{13}C NMR ($CDCl_3$) δ ppm 17.17, 21.32, 77.90, 122.58, 125.12, 125.94, 128.71, 128.77, 128.80, 130.38, 134.93, 136.28, 136.85, 143.98, 158.37. HRMS [ESI] calculated for $C_{17}H_{18}N_2O_2$ ($M+H^+$) 283.1441; found 283.1447.



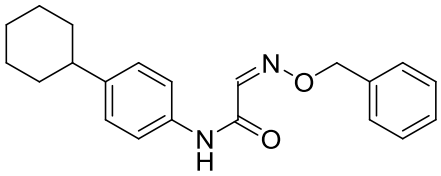
2-[(Benzyloxy)imino]-N-(3,5-dimethylphenyl)acetamide (7e)
Following the procedure for **7b** (Method B), compound **7e** was produced in 87% yield. ^{1}H NMR ($CDCl_3$) δ ppm 2.33 (s, 6H), 5.28 (s,2H), 6.80 (s,1H), 7.23 (s, 2H), 7.37-7.45 (m, 5H), 7.56 (s, 1H), 8.14 (br.s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 20.98, 40.94, 77.30, 117.18, 126.02, 127.96, 128.27, 135.75, 136.42, 138.44, 143.54, 158.82. HRMS [ESI] calculated for $C_{17}H_{18}N_2O_2$ ($M+H^+$) 283.1441; found 283.1438.



2-[(Benzyloxy)imino]-N-[4-(propan-2-yl)phenyl]acetamide (7f)
Following the procedure for **7a** (Method A), compound **7f** was produced in 93% yield. ^{1}H NMR ($CDCl_3$) δ ppm 1.25 (d, 6H), 2.90 (cm, 1H), 5.28 (s, 2H), 7.22 (d, 2H, J=8.4Hz), 7.32-7.60 (cm, 5H), 7.5 (d,2H, J=8.4Hz), 7.57 (s,1H), 8.17 (br.s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 24.00, 33.64, 77.70, 120.01, 126.99, 128.36, 128.52, 128.66, 134.66, 136.16, 143.89, 145.44, 159.23. HRMS [ESI] calculated for $C_{18}H_{20}N_2O_2$ ($M+H^+$) 297.1598; found 297.1596.

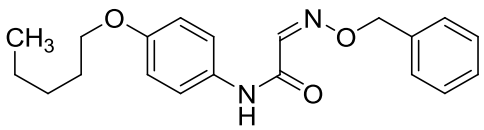


2-[(Benzyloxyimino)]-N-(4-tert-butylphenyl)acetamide (7g)
Following the procedure for **7b** (Method B), compound **7g** was produced in 88% yield. ^{1}H NMR ($CDCl_3$) δ ppm 1.32 (s, 9H), 5.28 (s, 2H), 7.33-7.46 (m, 7H), 7.51 (d, 2H, J = 8.0 Hz), 7.58 (s, 1H), 8.18 (br.s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 31.29, 34.43, 77.70, 119.68, 125.92, 128.37, 128.53, 128.66, 134.35, 136.15, 143.88, 147.71, 159.26. HRMS [ESI] calculated for $C_{14}H_{22}N_2O_2$ ($M+H^+$) 311.1754; found 311.1761.



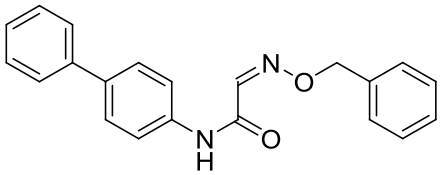
2-[(benzyloxy)imino]-N-(4-cyclohexylphenyl)acetamide (7h)
Following the procedure for **7b** (Method B), compound **7h** was produced in 89% yield. ^{1}H NMR ($CDCl_3$) δ ppm 1.15-1.45 (cm, 5H), 1.60-1.95 (cm, 5H), 2.50 (m, 1H), 5.28 (s, 2H), 7.20 (d, 2H, J=7.2Hz), 7.34-7.45 (cm, 5H), 7.50 (d, 2H, J=7.2Hz), 7.57 (s,1H), 8.17 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 26.13, 26.87, 34.49, 44.05, 77.69, 119.96, 127.37,

128.36, 128.52, 128.66, 134.66, 136.16, 143.89, 144.70, 159.21. HRMS [ESI] calculated for $C_{21}H_{24}N_2O_2$ ($M+H^+$) 337.1911; found 337.1912.



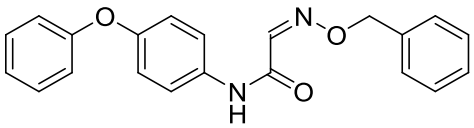
2-[(Benzyloxy)imino]-N-[4-(pentyloxy)phenyl]acetamide (7i)

Following the procedure for **7b** (Method B), compound **7i** was produced in 80% yield. ^{1}H NMR ($CDCl_3$) δ ppm 0.93 (t, 3H), 1.3-1.5 (m, 4H), 1.73-1.84 (m, 2H), 3.90 (t, 2H), 5.25 (s, 2H), 6.88 (d,2H, J=8.95Hz), 7.33-7.43 (cm, 5H), 7.47 (d, 2H, J=8.95Hz), 7.56 (s, 1H), 8.1 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 13.64, 22.08, 27.80, 28.57, 67.89, 77.24, 114.46, 121.21, 127.93, 128.10, 128.26, 129.51, 135.80, 143.51, 155.84, 158.74. HRMS [ESI] calculated for $C_{20}H_{24}N_2O_3$ ($M+H^+$) 341.1860; found 341.1860.



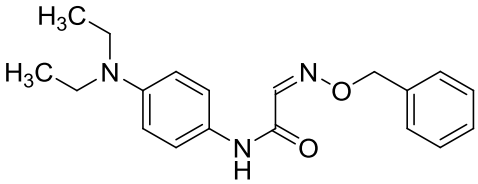
2-[(Benzyloxy)imino]-N-(4-phenylphenyl)acetamide (7j)

Following the procedure for **7a** (Method A), compound **7c** was produced in 46% yield. ^{1}H NMR ($CDCl_3$) δ ppm 5.31 (s, 2H), 7.30-7.50 (cm, 8H), 7.56-7.64 (cm, 5H), 7.64-7.72 (m, 2H), 8.29 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 77.39, 119.75, 126.47, 126.82, 127.32, 127.97, 128.18, 128.30, 128.42, 135.71, 135.88, 137.13, 140.00, 143.39, 158.93. HRMS [ESI] calculated for $C_{21}H_{18}N_2O_2$ ($M+H^+$) 331.1441; found 331.1454.



2-[(Benzyloxy)imino]-N-(4-phenoxyphenyl)acetamide (7k)

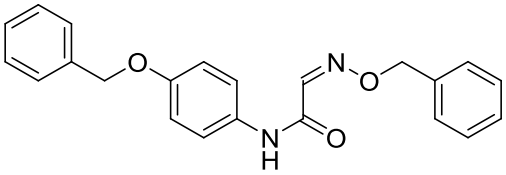
Following the procedure for **7a** (Method A), compound **7k** was produced in 60% yield. ^{1}H NMR ($CDCl_3$) δ ppm 5.29 (s, 2H), 6.96-7.06 (cm, 4H), 7.12 (t, 1H), 7.30-7.46 (cm, 7H), 7.51-7.62 (m, 3H), 8.20 (br.s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 77.34, 118.13, 119.24, 121.17, 122.79, 127.94, 128.15, 128.28, 129l.36, 132.04, 135.71, 143.35, 153.40, 157.02, 158.85. HRMS [ESI] calculated for $C_{21}H_{18}N_2O_3$ ($M+H^+$) 347.1390; found 347.1403.



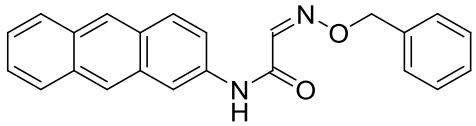
2-[(Benzyloxy)imino]-N-[4-(diethylamino)phenyl]acetamide (7l)

Following the procedure for **7b** (Method B), compound **7l** was produced in 79% yield. ^{1}H ($CDCl_3$) δ ppm 1.17 (t, 6H), 3.35 (q, 4H), 5.27 (s, 2H), 6.67 (d, 2H, J=8.98Hz), 7.3-7.5 (m, 7H), 7.58 (s, 1H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 12.14, 44.13, 77.13,

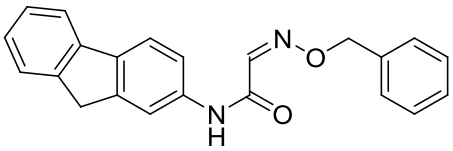
111.85, 121.63, 125.18, 127.94, 128.05, 128.23, 135.91, 143.76, 145.03, 158.54. HRMS [ESI] calculated for $C_{19}H_{25}N_3O_2$ ($M+H^+$) 326.1863; found 326.1850.



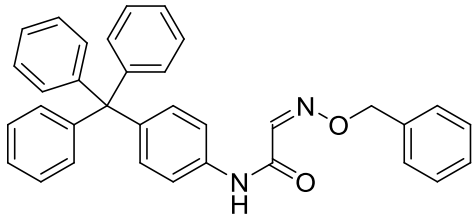
EXTRA: 2-[(benzyloxy)imino]-N-[4-(benzyloxy)phenyl]acetamide (7m)
Following the procedure for **7b** (Method B), compound **7m** was produced in 89% yield. ^{1}H NMR ($CDCl_3$) δ ppm 5.08 (s, 2H), 5.28 (s, 2H), 6.97 (d, 2H, J = 8.0 Hz), 7.3-7.45 (cm, 10H), 7.50 (d, 2H, J = 8.0 Hz), 7.58 (s, 1H), 8.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 69.90, 77.27, 114.91, 121.21, 127.08, 127.61, 127.94, 128.12, 128.21, 128.27, 129.95, 135.78, 136.49, 143.47, 155.42, 158.77. HRMS [ESI] calculated for $C_{22}H_{20}N_2O_3$ ($M+H^+$) 361.1547; found 361.1551.



N-(Anthracen-2-yl)-2-[(benzyloxy)imino]acetamide (7n)
Following the procedure for **7b** (Method B), compound **7n** was produced in 61% yield. ^{1}H NMR ($CDCl_3$) δ ppm 5.31 (s, 2H), 7.40-7.55 (m, 10H), 7.65 (s, 1H), 8.00-8.01 (m, 2H), 8.40-8.41 (m, 2H), 8.50 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 77.83, 115.90, 120.33, 125.20, 125.70, 125.87, 126.17, 127.98, 128.19, 128.38, 128.71, 129.29, 129.41, 129.85, 131.28, 131.78, 132.27, 133.68, 136.11, 143.83, 159.52. HRMS [ESI] calculated for $C_{23}H_{18}N_2O_2$ ($M+Na^+$) 337.1260; found 3371265.



2-[(Benzyloxy)imino]-N-(9H-fluoren-2-yl)acetamide (7o)
Following the procedure for **7b** (Method B), compound **7o** was produced in 71% yield. ^{1}H NMR ($CDCl_3$) δ ppm 3.91 (s, 2H), 5.28 (s, 2H), 7.29 (d, 1H, J = 8.0 Hz), 7.32-7.48 (cm, 7H), 7.53 (d, 1H, J = 8.0 Hz), 7.59 (s, 1H), 7.68-7.77 (m, 2H), 7.94 (s, 1H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 36.65, 77.36, 116.37, 118.23, 119.20, 119.81, 124.61, 126.06, 126.43, 127.97, 128.16, 128.30, 135.43, 135.75, 138.04, 140.84, 142.81, 143.50, 144.02, 158.85. HRMS [ESI] calculated for $C_{22}H_{18}N_2O_2$ ($M+H^+$) 343.1441; found 343.1451.



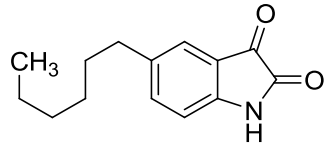
Following the procedure for **7b** (Method B), compound **7p** was produced in 87% yield.

2-[(Benzyloxy)imino]-N-[4-(triphenylmethyl)phenyl]acetamide (7p)

^{1}H NMR ($CDCl_3$) δ ppm 5.27 (s, 2H), 7.50-7.32 (m, 16H), 7.33-7.43 (m, 6H), 7.47 (d, 2H, J = 8.0 Hz), 7.56 (s, 1H), 8.19 (s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 40.69, 64.22, 77.35, 118.51, 125.58, 127.14, 127.99, 128.15, 128.27, 130.69, 131.42, 135.70, 142.87, 143.35, 146.26, 158.91. HRMS [ESI] calculated for $C_{34}H_{28}N_2O_2$ ($M+H^+$) 497.2224; found 497.2247.

General Procedure for the synthesis of the isatins (9-14)

A. Sulfuric acid Method:

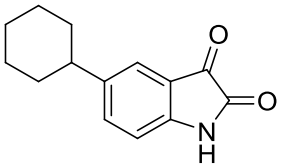


5-Hexyl-2,3-dihydro-1H-indole-2,3-dione (9)

A round-bottom flask is charged with concentrated sulfuric acid (33 ml) and is magnetically stirred at 50 °C open to the atmosphere. To the acid was added 2-[(benzyloxy)imino]-N-(4-*n*-hexylphenyl) (11 g, 32.5 mmole) in portions over 30 minutes. On completion of the addition the mixture was heated at 80 °C for an additional 10 minutes then allowed to cool to room temperature. The dark viscous solution was subsequently added in portions with rapid stirring to ice (750 ml). The crude product was isolated by vacuum filtration, and the filter cake washed with water. The crude product was dried under vacuum to give 6.3 g (85 %) of an orange solid.

^{1}H NMR ($CDCl_3$) δ ppm 0.87 (br t, 3H), 1.29 (m, 6H), 1.5-1.7 (m, 2H), 2.58 (t, 2H, J = 8.0 Hz), 6.82 (d, 1H, J=8.0 Hz), 7.37 (d, 1H, J=8.0 Hz), 7.44 (s,1H), 8.01 (br.s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 14.04, 22.54, 28.67, 31.16, 31.60, 35.09, 112.23, 118.15, 125.40, 138.77, 139.06, 147.20, 159.80, 183.38. HRMS [ESI] calculated for $C_{14}H_{17}NO_2$ ($M+H^+$) 232.1337; found 232.1332.

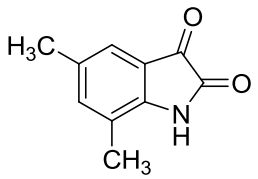
B. Methanesulfonic acid Method:



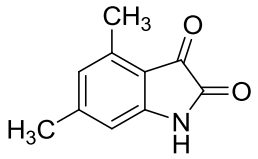
5-Cyclohexyl-2,3-dihydro-1H-indole-2,3-dione (10)

A round bottom flask is charged with methanesulfonic acid (6 ml) and is magnetically stirred at 50 °C open to the atmosphere. To the acid was added 2-[(benzyloxy)imino]-N-(4-cyclohexylphenyl) (0.567 g, 1.68mmole) in portions over 15 minutes. On completion of the addition the mixture was heated at 80 °C for an additional 10 minutes then allowed to cool to room temperature. The dark viscous solution was subsequently added in portions with rapid stirring to ice (150 ml). The crude product was isolated by vacuum filtration, and the filter cake washed with water. The crude product so isolated (0.535 g) was dried under vacuum then suspended in a three fold excess of 1N sodium hydroxide (7ml). After stirring for 1 hour the mixture was vacuum filtered and the filter cake rinsed with water. The combined filtrates were acidified with excess 2N hydrochloric acid and

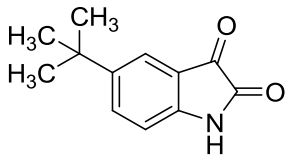
the semi-crude product isolated by vacuum filtration. The cake was water washed and dried in vacuo. Pure isatin was obtained by chromatography eluting with an ethyl acetate – hexane gradient to give the title compound as an orange-red crystalline solid (0.227 g, 60 %).
^{1}H NMR ($CDCl_3$) δ ppm 1.10-1.50 (cm, 5H), 1.70-1.95 (cm, 5H), 2.5 (m, 1H), 6.86 (d, 1H, J=8.0Hz), 7.42 (dd, 1H, J=8.0Hz, J=1.4Hz), 7.48 (s, 1H), 8.43 (br.s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 25.90, 26.65, 34.30, 43.79, 112.18, 118.19, 123.90, 137.48, 144.35, 147.21, 159.75, 183.33. HRMS [ESI] calculated for $C_{14}H_{15}NO_2$ ($M+H^+$) 230.1179; found 22301176.



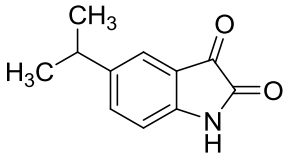
5,7-Dimethyl-2,3-dihydro-1H-indole-2,3-dione (11)
Following the procedure for **9** (H_2SO_4), compound **11** was produced in 60% yield.
^{1}H NMR ($CDCl_3$) δ ppm 2.35 (s, 3H), 2.32 (s, 3H), 7.23 (s, 1H), 7.29 (s, 1H), 8.35 (br.s, 1H). ^{13}C NMR (DMSO-d_6) δ ppm 15.31, 19.97, 117.51, 127.32, 122.09, 131.76, 140.04, 147.09, 160.00, 184.86. HRMS [ESI] calculated for $C_{10}H_9NO_2$ ($M+H^+$) 176.0706; found 176.0714.



4,6-Dimethyl-2,3-dihydro-1H-indole-2,3-dione (12)
Following the procedure for **9** (H_2SO_4), compound **12** was produced in 46% yield.
^{1}H NMR (DMSO-d_6) δ ppm 2.3 (s, 3H), 2.4 (s, 3H), 6.5 (s, 1H), 6.7 (s, 1H), 10.94 (s, 1H). ^{13}C NMR (DMSO-d_6) δ ppm 17.84, 22.53, 110.59, 114.22, 125.88, 140.08, 150.04, 151.62, 160.20, 184.51. HRMS [ESI] calculated for $C_{10}H_9NO_2$ ($M+H^+$) 176.0706; found 176.0712.



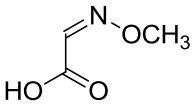
5-tert-Butyl-2,3-dihydro-1H-indole-2,3-dione (13)
Following the procedure for **10** (CH_3SO_3H), compound **13** was produced in 64% yield.
^{1}H NMR ($CDCl_3$) δ ppm 1.33 (s, 9H), 6.88 (d, 1H, J=8.25Hz), 7.63 (dd, 1H, J=8.25Hz, J=2.1Hz), 7.68 (d, 1H, J=1.9Hz), 8.17 (br.s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 31.16, 34.64, 112.06, 117.91, 122.71, 135.94, 147.04, 147.55, 159.96, 183.58. HRMS [ESI] calculated for $C_{12}H_{13}NO_2$ ($M+H^+$) 204.1019; found 204.1013.



5-(Propan-2-yl)-2,3-dihydro-1H-indole-2,3-dione (14)

Following the procedure for **10** (CH_3SO_3H), compound **14** was produced in 40% yield. ^{1}H NMR ($CDCl_3$) δ ppm 1.25 (d, 6H, J = 7.2 Hz), 2.9 (septet, 1H, J = 7.2 Hz), 6.85 (d, 1H, J = 8.0 Hz), 7.42 (d, 1H, J = 8.0 Hz), 7.52 (s,1H), 7.84 (br.s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 23.78, 33.54, 112.33, 118.17, 123.50, 137.15, 145.10, 147.33, 159.92, 183.46. HRMS [ESI] calculated for $C_{11}H_{11}NO_2$ ($M+H^+$) 190.0863; found 190.0855.

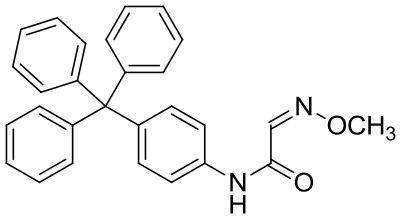
5-Tritylisatin (15):



2-[(Methyloxy)imino]acetic acid (6c)

The literature procedure[10] was followed using O-methylhydroxylamine hydrochloride to give the product as a semi-crystalline compound.

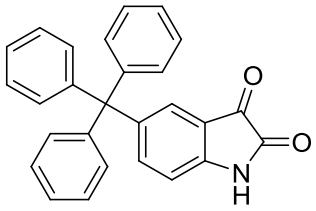
^{1}H NMR ($CDCl_3$) δ ppm 4.07 (s, 3H), 7.49 (s, 1H), 11.63 (br s, 1H).



2-[(Methoxy)imino]-N-[4-(triphenylmethyl)phenyl]acetamide (15)

A solution of acid **6c** (0.56 g, 5.43 mmol, 1.75 eq.), hydroxybenzotriazole (1.1 g, 8.1 mmol, 2.6 eq.), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC) (1.55 g, 8.1 mmol, 2.6 eq.) in DCM (ml) was stirred under nitrogen at 25 ^{o}C for 10 min. To the clear solution was added 4-tritylaniline (1.04 g, 3.1 mmol, 1 eq.) and diisopropylethylamine (1.6 g, 12.4 mmol, ml, 4 eq.) were added simultaneously to the reaction mixture. After 2 h slow precipitation was seen, and TLC analysis (20% EtOAc/Hex) showed 50% complete reaction. The reaction was stirred for 48 h, quenched with saturated sodium bicarbonate. The mixture was filtered, and the solid was vacuum dried to give pure product (0.47 g). The organic layer was separated, washed with water, brine, dried over sodium sulfate, and the solvents were evaporated. Addition of DCM (10-20 ml) allowed for another crop of product to be filtered (0.42 g). The remaining material was purified via chromatography using 10-20% EtOAc/Hexanes to give product (0.2 g). Total combined yield of the lots was 1.09 g (83%) white solid.

^{1}H NMR (DMSO-d_6) δ ppm 3.97 (s, 3H), 7.09 (d, 2H, J = 8.8 Hz), 7.14 (d, 6H, J = 7.5 Hz), 7.20 (t, 3H, J = 7.5 Hz), 7.30 (t, 6H, J = 7.5 Hz), 7.58 (d, 2H, J = 8.8 Hz), 7.74 (s, 1H), 10.35 (br s, 1H); ^{13}C NMR (d6-DMSO) δ ppm 62.49, 64.05, 119.05, 125.92, 125.67, 130.39, 130.80, 136.01, 141.98, 144.18, 146.37, 158.95. HRMS [ESI] calculated for $C_{28}H_{24}N_2O_2$ ($M+H^+$) 421.1911; found 421.1914.



5-(Triphenylmethyl)-2,3-dihydro-1H-indole-2,3-dione (16)

A round-bottom flask was charged with polyphosphoric acid (5 ml) and is magnetically stirred at 100 °C open to the atmosphere. To the acid was added 2-[(methoxy)imino]-N-[4-(triphenylmethyl)phenyl]acetamide (**15**) (0.24 g, 0.57 mmole) in portions over 15 minutes. On completion of the addition the mixture was heated at 100 °C for an additional 1.5 h then allowed to cool to room temperature. The dark viscous solution was subsequently added in portions with rapid stirring to ice (80 ml). The aqueous suspension was extracted with DCM (3 x 15 ml),and the organic layer was separated, washed with saturated sodium bicarbonate, water, and then dried over sodium sulphate. The solvents were evaporated to give an orange-brown solid (0.148 g, 67%) of sufficient purity for analysis.

^{1}H NMR ($CDCl_3$) δ ppm 6.79 (d, 1H, J = 8.00 Hz), 7.19-7.29 (m, 15 H), 7.45 (dd, 1H, J = 8.3, 2.0 Hz), 7.56 (s, 1H), 7.69 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm 64.72, 111.95, 117.51, 126.60, 127.92, 128.11, 131.02, 142.03, 143.79, 146.02, 147.64, 160.26, 183.44. HRMS [ESI] calculated for $C_{27}H_{19}NO_2$ ($M+H^+$) 390.1489; found 390.1493.