The Alkylation of Isatin-Derived Oximes: Spectroscopic and X-Ray Crystallographic Structural Characterization of Oxime and Nitrone Products

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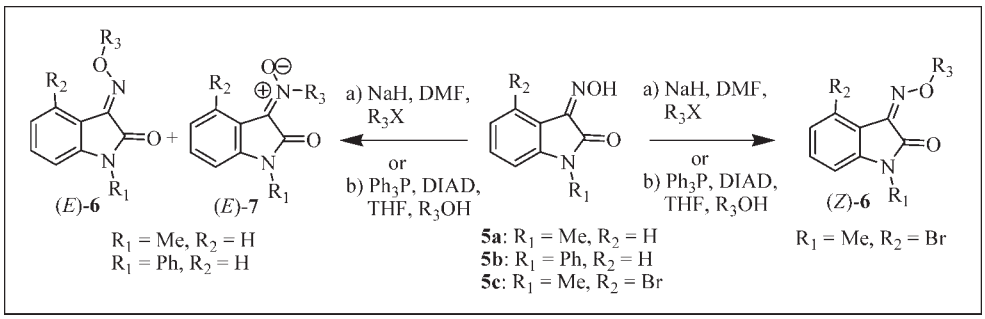

A series of isatin oximes was alkylated with alkyl halides and under Mitsunobu conditions to generate *O*-alkylated oxime ether and *N*-alkylated nitrone products. Alkylation of the sodium salts of oximes **5a** and **5b** with alkyl iodides produced predominantly the *N*-alkylated nitrones (*E*)-**7** while alkylation of **5a** and **5b** with the harder electrophiles alkyl bromides and alkyl chlorides, gave mostly the *O*-alkylated products, oxime ethers (*E*)-**6**. Interestingly, alkylation of oxime **5b** under Mitsunobu conditions with isopropyl alcohol produced the *N*-alkylated nitrone (*E*)-**7bd** as the major product. However, alkylation of oxime **5c**, which incorporates a sterically bulky bromine substituent at the C-4 position of the isatin heterocycle, with 2-bromo- and 2-iodo-propane or with isopropyl alcohol under Mitsunobu conditions gave exclusively the *O*-alkylated product, oxime ether (*Z*)-**6cd**. The oxime ether and nitrone products **6** and **7**, respectively, were characterized by LC/MS, ^{1}H NMR, and ^{13}C NMR. In addition, the structures of oxime ether (*E*)-**6bd** and nitrone (*E*)-**7ad** were determined by X-ray crystallography.

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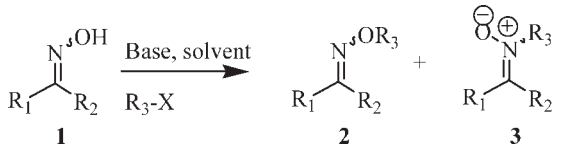
INTRODUCTION

Oximes (**1**) are important synthetic intermediates in organic synthesis that have also found application in a medicinal chemistry setting. As a synthetically useful functionality, oximes can be used to protect carbonyl groups, reduced to an amine or, in the case of oximes derived from aldehydes, undergo dehydration to a nitrile [1]. During the course of our survey of small molecule inhibitors of respiratory syncytial virus (RSV) fusion, we were interested in probing the potential of isatin-derived oximes as bioisosteres of the benzimidazol-2-one template that has provided a series of potent antiviral agents [2]. Isatin derivatives have found wide application as scaffolds in medicinal chemistry, including a series of Schiff bases and hydrazones evaluated as potential anticonvulsants [3] and cyclin-dependent kinase-2 inhibitors [4]. In addition, a number of isatin and oxindole derivatives demonstrate antiviral properties, exemplified by inhibitors of poxvirus [5], ectromelia [6], rhinovirus [7], HIV-1 [8], and the coronavirus responsible for severe acute respiratory syndrome (SARS) [9]. Oximes have been examined as useful pharmacophores in a range of therapeutic agents that encompass multiple disease areas. For example, oxime derivatives have been evaluated as dual agonists of peroxisome proliferator-activated receptors (PPARs) α and γ for the treatment of type II diabetes [10], vascular endothelial growth factor (VEGF)-2 kinase inhibitors as antiproliferative agents [11], *N*-methyl-D-aspartate (NMDA) [12] and AMPA/kainite [13] receptor antagonists, and γ-aminobutyric acid (GABA) uptake inhibitors as potential anticonvulsants [14]. A particularly prominent oxime ether derivative

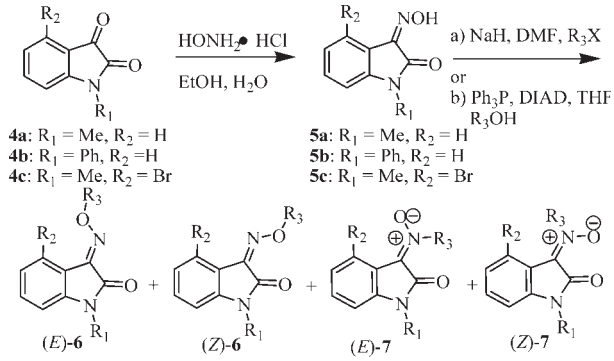
Scheme 1. Alkylation of oximes of general structure **1**.



that has been evaluated in clinical trials as an antiviral agent for the treatment of HIV infection is SCH 351125, an orally bioavailable CCR5 receptor antagonist [15].

To establish the potential of isatin-derived oxime ethers as RSV fusion inhibitors, a parallel synthesis approach was envisioned as a means of rapidly generating a series of isatin oxime ethers **6** from oximes **5** by a simple alkylation procedure. However, it is well established that the alkylation of oximes of general structure **1** can produce *O*-alkyloxime-ethers **2** and *N*-alkylated nitrones **3**, as shown in Scheme 1, depending upon the site at which alkylation occurs [16,17]. The ratio of *O*- to *N*-alkylated products can be influenced by several factors, including the geometry of the oxime salts derived from **1**. For example, alkylation of an *(E)*-aldoxime sodium salt with alkyl halides produced mainly the *O*-alkylated oximes but alkylation of the (*Z*)-aldoxime sodium salt with the same series of electrophiles produced similar amounts of the *N*- and *O*-alkylated products [17]. Whilst there are many reports in the literature of oxime alkylation procedures, there has not been a systematic study of the alkylation of isatin oximes **5** and structural characterization of the possible products, the oxime ethers **6** and nitrones **7**. The alkylation of oxime **5** is potentially a complex process since four products can be formed: *(E)*- and (*Z*)-oximes **6** and *(E)*- and (*Z*)-nitrones **7**, and it was anticipated that product distribution would show some dependence on the reagents, the reaction conditions, and the substitution patterns of the aryl ring. In this article, we report the results of studies of the alkylation of a series of isatin oximes **5** and characterization of the products by LC/MS, ^{1}H NMR, ^{13}C NMR and, for select examples, X-ray crystallography.

Scheme 2. Alkylation of isatin oximes.



RESULTS AND DISCUSSION

The procedures for the preparation and alkylation of isatin oximes **5** are summarized in Scheme 2. Isatin oximes **5a-c** were readily obtained from isatins **4a–c** by treatment with $NH_2OH{\cdot}HCl$ in aqueous EtOH. Isatins **4a** and **4b** were available from commercial sources and *N*-methyl-4-bromo isatin (**4c**) was obtained by alkylation of commercially available 4-bromoisatin with methyl iodide in the presence of K_2CO_3 as the base. Alkylation of **5a** and **5b** by deprotonation with NaH in DMF and exposure to alkyl halides gave mixtures of isatin *O*-alkyloxime ethers *(E)*-**6** and nitrones *(E)*-**7**, with the distribution of the products for each reaction summarized in Tables 1 and 2. DMF was chosen as the solvent to

Table 1

Alkylation of isatin oxime **5a** with alkyl halides to give *O*-alkylated oxime ethers and *N*-alkylated nitones.

No.	Oxime	Nitrone	Electrophile	R_1	R_2	R_3	Ratio of oxime: nitrone (%)[b]	Total yield (%)	Rxn time (h)
1	(*E*)-**6aa**[a]	(*E*)-**7aa**[a]	MeI	Me	H	Me	36:64	64[c]	15
2	(*E*)-**6ab**	(*E*)-**7ab**	EtI	Me	H	Et	40:60	90	15
3	(*E*)-**6ac**	(*E*)-**7ac**	nPrI	Me	H	nPr	37:63	91	15
4	(*E*)-**6ad**	(*E*)-**7ad**	iPrI	Me	H	iPr	40:60	89	15
5	(*E*)-**6ae**	(*E*)-**7ae**	$(CH_3CH_2)_2CH$ Br	Me	H	$(CH_3CH_2)_2CH$	57:43	97	15
6	(*E*)-**6af**	(*E*)-**7af**	cPentyl Iodide	Me	H	cPen	58:42	97	15
7	(*E*)-**6ag**	(*E*)-**7ag**	cHexyl Iodide	Me	H	cHex	50:50	94[c]	15
8	(*E*)-**6ah**	(*E*)-**7ah**	4-$OMeC_6H_4$ CH_2Cl	Me	H	CH_2-Ph-4′-OMe	58:42	64	15
9	(*E*)-**6ai**	(*E*)-**7ai**	$BrCH_2CO_2tBu$	Me	H	CH_2CO_2tBu	90:10	91	15

[a] Letter designations: the first letter represents the substitution pattern on the isatin ring system, whereas the second letter discriminates the different substitutions on the oxime oxygen and nitrone nitrogen.

[b] Ratios between isomers were determined by weights after flash column chromatography, except, entry 1 where the ratio was determined by HPLC since the two products were not separable.

[c] Yields based on 10 and 34% recovered starting material for entries 1 and 7, respectively.

Table 2

Alkylation of **5b** with isopropyl halides under basic conditions and with isopropyl alcohol under Mitsunobu conditions to give *O*-alkylated oxime ether *(E)*-**6bd** and *N*-alkylated nitone *(E)*-**7bd**.

No.	Reagent used[a]	Oxime (*E*)-**6bd**[b] (%)	Nitrone (*E*)-**7bd**[b] (%)	Total yield (%)	Rxn time (h)
1	iPrI	43 (48)	57 (52)	83	15
2	iPrBr	54 (62)	46 (38)	86	15
3	iPrCl	65 (70)	35 (30)	61[c]	76
4	iPrOH	12 (16)	88 (84)	84	18

[a] Alkylation of oxime **5b** with alkyl halides in the presence of NaH and under Mitsunobu reaction conditions with isopropyl alcohol for entries 1–3 and entry 4, respectively.
[b] Isomeric product ratios were determined by weight after purification by flash column chromatography. Ratios in parentheses were determined by integration of HPLC peaks.
[c] Yield based on 6% recovered starting material.

ensure high solubility of the isatin oximes **5a** and **5b** and their sodium salts during the course of the reaction, since heterogeneous reaction conditions caused by the precipitation of oxime salts from solvents such as acetone or toluene have been reported to influence the ratio of products formed [16]. The effect of the counter ion on product distribution was also examined, with lithium, potassium, and tetramethylammonium salts evaluated in addition to sodium [16]. Furthermore, the application of the Mitsunobu reaction to this process was also studied. Several *O*-alkylated isatin oxime ethers were also obtained by combining isatins **4a–c** with *O*-alkylated hydroxylamine hydrochloride salts in aqueous EtOH for the purpose of comparison with the products obtained from the alkylation reactions.

The results of these studies, compiled in Table 1, reveal that the reaction yields are generally excellent, ranging from 64 to 97% and that product distribution between the *O*- and *N*-alkylated products is dependent on the nature of the electrophile. When soft electrophiles such as alkyl iodides were employed, the *N*-alkylated products, isatin nitrones *(E)*-**7**, were favored slightly over the *O*-alkylated oxime ethers **6**, with the ratio ranging from just over 1:1 to 2:1 (Table 1, Entries 1–4 and 7). 2-Iodocyclopentane provided an exception, producing a 58:42 ratio of oxime to nitrone, respectively (Table 1, Entry 6). However, with harder electrophiles, such as alkyl bromides (Table 1, Entries 5 and 9) and alkyl chlorides (Table 1, Entry 8), this trend was largely reversed with the *O*-alkylated products predominating, in the range of 3:2 to 9:1.

The effect of the nature of the alkyl halide on the ratio of *O*- and *N*-alkylated products formed in base-catalyzed processes was observed earlier with both benzophenone oxime [16] and aldoxime [17] systems. In those studies, the *O*-alkylated products predominated by three to ninefold, with alkyl chlorides providing the highest preference for *O*-alkylation. However, the studies were not conducted in a systematic fashion and correlation of the effect of hard and soft electrophiles on product distribution could not be fully appreciated. In addition, the study of aldoxime alkylation was complicated by the geometry of the aldoxime sodium salt which exerted a profound effect on the product ratio [17]. The *(E)*-aldoxime sodium salt was found to give the oxime ether by a preference of three to ninefold over the nitrone products, whereas the (*Z*)-aldoxime sodium salt showed little preference for *O*- *versus N*-alkylation, presumably a consequence of the reduced steric encumbrance around the nitrogen atom in this conformation.

To more closely evaluate the effect of the leaving group on the ratio of *O*- and *N*-alkylated product formation in the isatin oxime system, additional alkylation experiments were conducted with **5b** using 2-iodo-, 2-bromo-, and 2-chloro-propane, which afforded a mixture of *O*-alkyloxime ether *(E)*-**6bd** and the nitrone *(E)*-**7bd**. In addition, since the pKa of many oximes is similar to that of a phenol [18], alkylation of **5b** with isopropyl alcohol under the mild conditions associated with the Mitsunobu reaction was examined [19]. The results of this survey are compiled in Table 2 where the yields of products were generally high, 83–86%, except in the case of 2-chloropropane (Entry 3, 61% yield). The alkylation of **5b** with 2-chloropropane was a sluggish process, and the reaction was worked up after an extended, 76 h time interval. The data in Table 2 reveal a slight preference toward the *N*-alkylated nitrone *(E)*-**7bd** when the soft electrophile 2-iodopropane was employed. However, the *O*-alkylated product, ether *(E)*-**6bd**, predominated slightly when 2-bromopropane was used as the electrophile, and the ratio further amplified in the reaction of **5b** with 2-chloropropane. Interestingly, under Mitsunobu conditions, the oxime **5b** reacted with isopropyl alcohol to afford predominantly the *N*-alkylated nitrone *(E)*-**7bd** in a ratio of 88:12 over the *O*-alkylated oxime ether *(E)*-**6bd** (Table 2, Entry 4). To the best of our knowledge, this experiment represents the first example of oxime alkylation under Mitsunobu conditions affording a nitrone product.

Table 3

Key spectroscopic data for isatin oximes **6** and nitrones **7**.

	Oxime **6**/Nitrone **7**	^{1}H NMR of oxime and nitrone in $CDCl_3$		Chemical shift differences between oximes and nitrones	
Entry No.	Compound No.	C4 Ar-H (ppm)	Oxime CH*n*/Nitrone CH*n* (ppm)	ΔC4 Ar-H (ppm)	ΔOxime CH*n*/ Nitrone CH*n* (ppm)
1	(*E*)-**6ab**	7.96	4.52–4.56	−0.38	−0.27
	(*E*)-**7ab**	8.34	4.79–4.83		
2	(*E*)-**6ac**	7.95	4.44–4.47	−0.40	−0.31
	(*E*)-**7ac**	8.35	4.75–4.78		
3	(*E*)-**6ad**	7.93	4.69–4.80	−0.44	−1.58
	(*E*)-**7ad**	8.37	6.28–6.37		
4	(*E*)-**6ae**	7.94	4.44–4.46	−0.48	−1.69
	(*E*)-**7ae**	8.42	6.13–6.15		
5	(*E*)-**6af**	7.88	5.11–5.14	−0.47	−1.41
	(*E*)-**7af**	8.35	6.52–6.55		
6	(*E*)-**6ag**	7.96	4.50–4.54	−0.40	−1.46
	(*E*)-**7ag**	8.36	5.95–6.01		
7	(*E*)-**6ah**	7.88	5.44	−0.42	−0.44
	(*E*)-**7ah**	8.30	5.88		
8	(*E*)-**6ai**	8.06	4.93	−0.28	−0.52
	(*E*)-**7ai**	8.34	5.45		
9	(*E*)-**6bd**	8.05	4.78–4.87	−0.42	−1.52
	(*E*)-**7bd**	8.47	6.30–6.39		

The structures of the alkylated isatin oximes were determined by a combination of spectroscopic methods. The oxime ethers **6** could readily be distinguished from the nitrones **7** by examination of the infra red spectra. An earlier report identified unique N-O absorbances for the nitrone and oxime between 1170–1280 and 920–1005 cm^{-1}, respectively [16]. The IR spectrum of the oxime ether *(E)*-**6ad** exhibits the characteristic N-O band at 971 cm^{-1}, which is absent in the IR spectrum of the isomeric nitrone *(E)*-**7ad** (Table 1, Entry 4). Conversely, a unique nitrone N-O band appeared at 1241 cm^{-1} in the IR spectrum of nitrone *(E)*-**7ad** that is not exhibited by the oxime ether *(E)*-**6ad**.

The ^{1}H NMR spectra of oxime ethers **6** and nitrones **7** are generally quite similar with the exception of the chemical shifts for the C-4 aryl hydrogen atom and the protons on the carbon atoms attached to the oxime oxygen or nitrone nitrogen atoms. The ^{1}H NMR chemical shifts for the isatin C-4 aryl hydrogen, and the protons on the carbon atom attached to the oxime oxygen and nitrone nitrogen atoms are presented in Table 3. In the ^{1}H NMR, the C-4 aryl hydrogen of isatin nitrones **7** consistently resonates between 0.28 and 0.48 ppm downfield of the chemical shift of the same proton in the corresponding isatin oxime ethers **6**, attributed to a deshielding effect induced by the nitrone moiety. Similarly, the ^{1}H NMR chemical shifts for the protons on the carbon atom attached to the nitrone nitrogen atom in **7** resonate downfield of the protons on the carbon atom bound to the oxygen atom in the oxime ethers **6**. For the series of nitrones **7ab**, **7ac**, **7ah**, and **7ai** and their corresponding oxime ether isomers **6ab**, **6ac**, **6ah**, and **6ai**, compounds all prepared from primary alkyl halides, the ^{1}H NMR chemical shifts of the methylene protons differ by 0.27 to 0.52 ppm (Table 3, Entries 1, 2, 7, and 8). For nitrones **7ad**, **7ae**, **7af**, **7ag**, and **7bd** and oxime ethers **6ad**, **6ae**, **6af**, **6ag**, and **6bd**, derived from secondary alkyl halides, the differences in ^{1}H NMR chemical shifts of the methine protons are more pronounced, with a difference of 1.41 to 1.69 ppm (Table 3, Entries 3–6 and 9).

To provide further support for the structural assignments, a single crystal X-ray structure was obtained for the nitrone *(E)*-**7ad**, which indicates that this compound possesses an *(E)*-geometric configuration, as depicted in Figure 1. Attempts to recrystallize the corresponding oxime ether *(E)*-**6ad** for X-ray crystallographic structure determination to allow a direct comparison with *(E)*-**7ad** were unsuccessful. However, the solid state structure was determined for the close analogue, oxime ether *(E)*-**6bd** in which the isatin *N* substituent is phenyl rather than methyl and, as depicted in Figure 2, this compound also possesses the *(E)*-geometric configuration. In the *(E)*-configuration, the oxygen atoms of the oxime *(E)*-**6bd** and nitrone *(E)*-**7ad** project away from the carbonyl oxygen of the isatin amide moiety, presumably to optimize dipole interactions and minimize the lone pair-lone pair repulsion that would exist in the (*Z*)-oxime and lone pair-negative charge repulsions that would occur in the isomeric (*Z*)-nitrone (*vide infra*). In addition, the

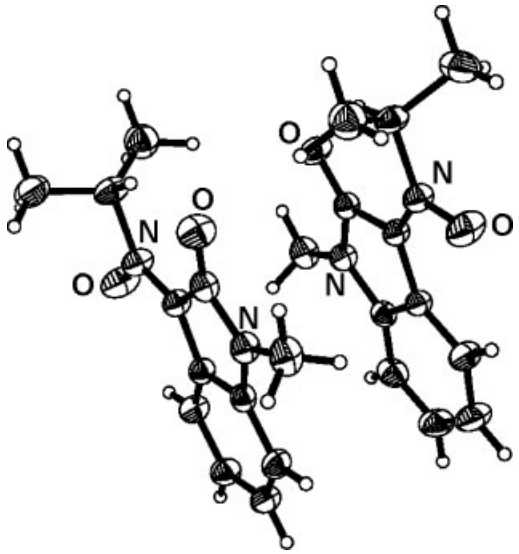


Figure 1. X-ray crystallographic structure of nitrone *(E)*-**7ad**.

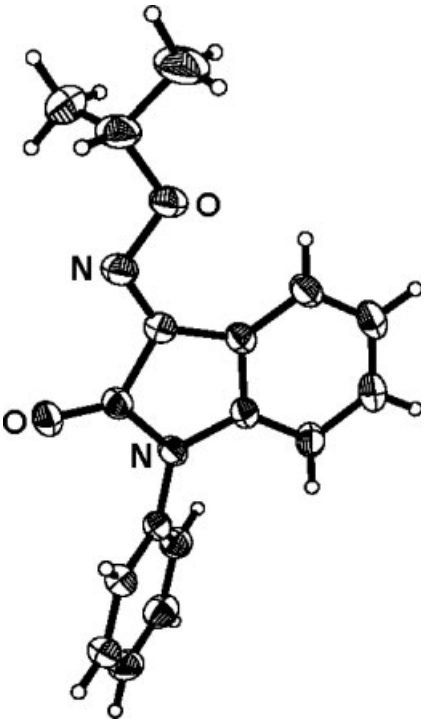


Figure 2. X-ray crystallographic structure of oxime ether*(E)*-**6bd**.

crystallographic structures indicate that the oxygen atom of both the oxime ether *(E)*-**6bd** and nitrone *(E)*-**7ad** are situated within hydrogen bonding distance of the C-4-aryl hydrogen, measured at 2.527 Å for *(E)*-**6bd** and 2.446 Å for *(E)*-**7ad**, respectively.

The X-ray crystallographic data for oxime ether *(E)*-**6bd** and nitrone *(E)*-**7ad** indicate without ambiguity that both are *(E)*-isomers. On the basis of the additional studies and *ab initio* calculations described below, we conclude that all of the oxime ethers and nitrones presented in Tables 1 and 2 most likely possess the *(E)*-geometric configuration.

The (*Z*)-isomers of either an oxime ether or nitrone analog were not isolated from any of the alkylation procedures, consistent with an earlier report that indicated that the nitrone (*Z*)-**7aa** could only be produced briefly when nitrone *(E)*-**7aa** was irradiated at a temperature maintained between 6 and 10°C [20,21]. However, warming to room temperature resulted in isomerization of (*Z*)-**7aa** to *(E)*-**7aa**. HPLC analysis of the products produced in the alkylation reaction that afforded oxime *(E)*-**6bd** and nitrone *(E)*-**7bd** indicated a trace of an additional peak with a retention time close to oxime *(E)*-**6bd** that may be the isomeric oxime, (*Z*)-**6bd**; however, this compound could not be isolated. In an attempt to increase the production of the (*Z*)-oxime isomer, direct oxime ether formation from isatin **4b** was examined. Condensation of **4b** with 1.2 equivalents of *O*-isopropylhydroxylamine hydrochloride in EtOH/H_2O gave a 96% yield of oxime product that was an 89:11 mixture of *(E)*-**6bd** and (*Z*)-**6bd** as determined by HPLC (Table 4, Entry 1). Oxime ethers *(E)*-**6bd** and *(Z)*-**6bd** were prepared in 95% yield under the same conditions but with an equimolar quantity of pyridine included to neutralize the HCl present in the reaction mixture in an attempt to reduce interconversion between the (*Z*) to *(E)* isomers (Table 4, Entry 2). Under these conditions, the

Table 4

Condensation of **4b** and **4c** with *O*-isopropyl hydroxylamine to give *(E)*- and (*Z*)-oxime ether **6**.

No.	(*E*)-Oxime	(*Z*)-Oxime	R_1	R_2	Ratio of isomer E:Z-oxime[a] (%)	Total yield (%)[d]
1	(*E*)-**6bd**	(*Z*)-**6bd**	Ph	H	89:11[b]	96
2	(*E*)-**6bd**	(*Z*)-**6bd**	Ph	H	93:7[b]	95
3	(*E*)-**6cd**	(*Z*)-**6cd**	Me	Br	43:57[c]	91

[a] R_3 = iPr for all entries.
[b] Ratio was determined by HPLC peak integration.
[c] Ratio was determined after isolation of the products by flash column chromatography.
[d] Total yield as a mixture.

Table 5

Ab initio calculations for nitrone and oxime ether geometric isomers.

Calculation Method	Nitrone:Δ[(*E*)-**7ad**—(*Z*)-**7ad**] (kcal/mol)	Oxime: Δ[(*E*)-**6ad**—(Z)-**6ad**] (kcal/mol)	Oxime:Δ[(*E*)-**6cd**—(*Z*)-**6cd**] (kcal/mol)
B3LYP/6-31G* (solvent: H_2O)	−6.9	−3.2	2.1
B3LYP-31G*// B3LYP-6-31+G* (solvent: H_2O)	−6.1	−3.5	2.3
B3LYP-31G*// B3LYP-aug-cc- pvdz (solvent: H_2O)	−5.6	−3.4	2.3

ratio of oxime ether *(E)*-**6bd** and (*Z*)-**6bd** was 93:7 by analytical HPLC, indicating that (*Z*) to *(E)* product isomerization was not a significant issue when the reaction was conducted under slightly acidic conditions. To further favor the formation of a (*Z*)-oxime isomer, a sterically bulky bromine substituent was introduced at the C-4 position of the isatin heterocycle. Condensation of *N*-methyl-4-bromoisatin (**4c**) with *O*-isopropylhydroxylamine hydrochloride in EtOH/H_2O produced two oxime ether products **6cd**, which were separable by silica gel column chromatography to give products in a ratio of 57:43. The ^{1}H NMR, ^{13}C NMR and LC/MS spectra of the two products were very similar but could be differentiated by close inspection of the data. In the ^{1}H NMR, the methine proton on the carbon atom attached to the oxygen atom of the oxime ether appears as a septet. For the minor oxime ether isomer, this methine proton resonance is centered at 4.77 ppm, which is slightly downfield of the methine proton for the major oxime ether isomer, centered at 4.74 ppm. The isatin *N*-Me protons resonate as singlets at 3.22 ppm for the minor isomer and 3.20 ppm for the major isomer, whereas the signal for the two methyl protons of the isopropyl group appear as doublets at 1.45 ppm for the minor isomer and 1.47 ppm for the major isomer. The minor product completely isomerized to the major oxime ether within an hour as a solution in $CDCl_3$ in an NMR tube. Although the minor isomer was readily recrystallized from a mixture of ether and hexanes at 4°C, the small rod crystals that resulted failed to diffract satisfactorily to allow a structure determination. An attempt to prepare oxime ether *(E)*-**6ad** from the bromo isatin oxime **6cd** by subjecting each one separately to a lithium-halogen exchange reaction followed by protonation to allow correlation with *(E)*-**6ad** was unsuccessful.

In an effort to illuminate further the issue of *(E)* and (*Z*) ratios, *ab initio* studies were conducted. Comparative analysis of *(E)*- and (*Z*)-oximes **6ad** and **6cd** and *(E)*- and (*Z*)-nitrones **7ad** were performed through geometry optimization and relative energy evaluation. The geometries were optimized using DFT at the B3LYP/6-31G* level of theory and basis set. The derived geometries were then used to perform corrections using B3LYP/6-31+G* and Dunning's aug-cc-PVDZ basis sets [22]. Both geometry optimizations and single point energy evaluations were performed in the presence of solvent (water) using the PCM method available in G03 [23]. The relative energies for nitrones *(E)*- and (*Z*)-**7ad**, and oximes *(E)*- and (*Z*)-**6ad**, and *(E)*- and (*Z*)-**6cd** are presented in Table 5. The conformational analysis calculation results presented in Table 5 reveal that the nitrone **7ad** with the *(E)*-geometric configuration is stabilized by 5.9–6.9 kcal/mole when compared to its (*Z*)-isomer due to an unfavorable dipole–dipole interaction between the negatively charged oxygen of the nitrone and the lone pair of electrons on the isatin carbonyl moiety in the (*Z*)-isomer. The experimentally measured dipole moments of a structurally similar pair of nitrone isomers that incorporate an α-carbonyl moiety are reported to differ by four units [21]. For example, the dipole moments for *(E)*-*N*-(2,2,5,5-tetramethyl-4-oxodihydrofuran-3(2H)-ylidene)methanamine oxide and its (*Z*)-isomer were determined in dioxane to be 1.09 ± 0.13 and 5.31 ± 0.11, respectively [21]. The significant energy difference between the *(E)*- and (*Z*)-nitrones **7ad** is consistent with earlier studies of the isomerization of nitrone *(E)*-**7aa** to (*Z*)-**7aa** upon irradiation and explains the difficulties encountered in isolating the nitrone (*Z*)-**7ad** due to its facile isomerization to *(E)*-**7ad** at room temperature [21]. For the oxime derivatives, repulsion between the lone pairs of electrons on the oxime oxygen atom and the isatin carbonyl moiety leads to *(E)*-**6ad** being the more stable isomer by 3.2–3.5 kcal/mole based on the three molecular calculation methods when compared with (*Z*)-**6ad**. However, in oxime (*Z*)-**6cd** where R_2 = Br, steric hindrance overrides the stereo electronic effects that dominate the geometry of oxime ether (*Z*)-**6ad**. Thus, the oxime ether (*Z*)-**6cd** is more stable by 2.1–2.3 kcal/mole over the *(E)*-isomer. The results of these calculations led us to assign the major product as oxime ether (*Z*)-**6cd** and the minor product as the *trans*-isomer, *(E)*-**6cd** (Table 4, Entry 3).

The insights associated with the effect of a Br substituent at C-4 of the heterocycle on oxime geometry prompted an examination of the effect of this substitution pattern on the outcome of oxime alkylation. Thus,

Table 6

Alkylation of isatin oxime **5c** with *iso*-propyl halides under basic conditions and isopropyl alcohol under Mitsunobu conditions to give *O*-alkylated (*Z*)-oxime ethers.

Entry No.	Reagent used	Oxime (*Z*)-**6cd** (%)	Total yield (%)[a]	Reaction time (h)
1	iPrI	100	90	18
2	iPrBr	100	91	18
3	iPrOH	100	85	18

[a] Isolated yield after silica gel chromatography purification.

N-methyl-4-bromoisatin oxime **5c** was alkylated with *iso*-propyl bromide and *iso*-propyl iodide under basic conditions and also reacted with isopropyl alcohol under Mitsunobu conditions with the result that the *O*-alkylated product (*Z*)-**6cd** was formed exclusively in high yield in all cases. These data are presented in Table 6 and the oxime ether (*Z*)-**6cd** prepared in these reactions was spectroscopically and chromatographically identical to the major oxime ether product (*Z*)-**6cd** prepared by condensing *N*-methyl-4-bromoisatin with *O*-isopropylhydroxylamine hydrochloride (Table 4, Entry 3). This result presumably reflects the development of unfavorable steric interactions between the nitrone *N* substituents and the C-4 bromine atom in the transition state and dominates the previously observed propensity for softer electrophiles to react at the oxime *N* atom.

In summary, alkylation of the sodium salts of a series of isatin oximes **5a** and **5b** with soft electrophiles such as iodoalkanes leads to a slight preference for the *N*-alkylated nitrone products, while harder electrophiles, such as bromo- and chloro-alkanes, preferentially produce *O*-alkylated oxime ether products. Under Mitsunobu conditions, isatin oximes **5b** underwent alkylation preferentially on nitrogen leading to a predominance of the nitrone products. The installation of a bromine atom at C-4 of the heteroaryl ring of oxime **5c** led to the exclusive formation of the (*Z*)-oxime ether, the steric interactions provided by the bromine atom overriding the inherent stereo electronic control exerted by the interaction between the oxime oxygen atom and the α-carbonyl moiety.

EXPERIMENTAL

General directions. ^{1}H- and ^{13}C NMR spectra were obtained at 500 MHz and 126 MHz NMR, respectively. The chemical shifts (δ) are recorded in parts per million (ppm) downfield from TMS. Unless otherwise noted, all NMR samples were prepared in $CDCl_3$. IR spectra were recorded on Perkin Elmer System 2000 FT-IR. Drying of the organic layer during work-up was carried out over anhydrous $MgSO_4$, followed by filtration. Column chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique [24]. Melting points are uncorrected.

Preparative procedures. ***3-(Hydroxyimino)-1-methylindolin-2-one (5a).*** To a slurry of 1-methylisatin (**4a**) (5.28 g, 31.77 mmol) in EtOH (50 mL) was added a solution of $NH_2OH{\cdot}HCl$ (3.31 g, 47.66 mmol) in H_2O (6 mL) and the resulting brown reaction mixture stirred at rt. After 3 h, the solvent was removed *in vacuo* to afford a greenish-yellow paste that was triturated with H_2O (50 mL), filtered, and washed with H_2O (50 mL). The greenish-yellow solid product was dried in a vacuum oven overnight to give **5a** (5.49 g, 98% yield), which was used without further purification, m.p. 193.0–195.5°C (lit. m.p. 193–197°C) [25]; ^{1}H NMR δ 3.25 (s, 3 H), 6.83 (d, J = 7.63 Hz, 1H), 7.08 (t, J = 7.48 Hz, 1H), 7.40 (t, J = 7.78 Hz, 1H), 8.06 (d, J = 7.32 Hz, 1H), 9.57 (s, 1 H); ^{13}C NMR δ 26.2, 108.5, 115.6, 117.6, 123.3, 128.4, 132.7, 144.6, 163.8; LC-MS, MS m/z 177 (M+H).

General alkylation procedure. To a solution of isatin oxime **5** in DMF (0.25*M*) was added 1.2 equivalents of NaH (60% dispersion in oil) followed after 10 min by 1.2 equivalents of an alkyl halide. The progress of the reaction was followed by TLC and LC/MS. When the reaction was complete, the mixture was diluted with EtOAc and washed with dilute aqueous HCl. The reaction of oximes **5** with 2-iodopropane and 2-bromopropane as electrophiles were typically complete after 0.5 and 2.5 h, respectively, as indicated by TLC and LC/MS. The color of the reaction mixture changed during the course of the reaction from an initial dark red, presumably due to the isatin oxime alkoxy anion, to a brown reaction mixture after the oxime alkoxy anion was consumed. However, both reaction mixtures were allowed to stir at room temperature for 15 h before work up. HPLC determination of the ratio of products of the reaction using 2-iodopropane after 0.5 and 15 h showed no change in the product ratio; thus, there was no interconversion of products under the reaction conditions up to 15 h.

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)ethanamine oxide ((E)-7ab). This compound was obtained as orange solid, m.p. 103.0–104.5°C; ^{1}H NMR δ 1.52 (t, J = 7.32 Hz, 3 H), 3.27 (s, 3 H), 4.81 (q, J = 7.32 Hz, 2 H), 6.82 (d, J = 7.63 Hz, 1 H), 7.09 (t, J = 7.63 Hz, 1 H), 7.36 (t, J = 7.63 Hz, 1 H), 8.33 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 13.4, 26.2, 42.5, 58.2, 107.8, 118.3, 123.2, 124.9, 131.4, 133.5, 141.1, 160.5; LC-MS, MS m/z 205 (M+H); *Anal*. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.75; H, 5.83; N, 13.60.

(E)-3-(ethoxyimino)-1-methylindolin-2-one ((E)-6ab). This compound was obtained as yellow solid, m.p. 76.0–77.0°C; ^{1}H NMR δ 1.44 (t, J = 7.17 Hz, 3 H), 3.23 (s, 3 H), 4.54 (q, J = 7.12 Hz, 2 H), 6.81 (d, J = 7.63 Hz, 1 H), 7.05 (t, J = 7.63 Hz, 1 H), 7.37 (dt, J = 7.78, 0.92 Hz, 1 H), 7.95 (d, J = 7.32 Hz, 1 H); ^{13}C NMR δ 14.8, 26.1, 73.0, 108.3, 116.0, 123.0, 127.8, 132.3, 143.6, 144.5, 163.8; LC-MS, MS m/z 205 (M+H); *Anal*. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.55; H, 5.67; N, 13.66.

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)propan-1-amine oxide ((E)-7ac). This compound was obtained as orange solid, m.p. 76.5–78.0°C; ^{1}H NMR δ 1.01 (t, J = 7.48 Hz, 3 H), 1.95–2.03 (m, 2 H), 3.27 (s, 3 H), 4.76 (t, J = 7.32 Hz, 2 H), 6.82 (d, J = 7.63 Hz, 1 H), 7.09 (t, J = 7.63 Hz, 1 H), 7.37 (dt, J = 7.78, 1.22 Hz, 1 H), 8.35 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 11.0, 22.0, 26.2, 64.3, 107.7, 118.2, 123.1, 124.9,

131.4, 134.1, 141.0, 160.6; LC-MS, MS m/z 219 (M+H); *Anal*. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.03; H, 6.24; N, 12.79.

(E)-1-methyl-3-(propoxyimino)indolin-2-one ((E)-6ac). This compound was obtained as yellow solid, m.p. 53.0–54.5°C; ^{1}H NMR δ 1.01 (t, J = 7.32 Hz, 3 H), 1.81–1.89 (m, 2 H) 3.23 (s, 3 H), 4.45 (t, J = 6.56 Hz, 2 H), 6.81 (d, J = 7.93 Hz, 1 H), 7.06 (t, J = 7.48 Hz, 1 H), 7.38 (t, J = 7.78 Hz, 1 H), 7.95 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 10.3, 22.6, 26.1, 79.0, 108.4, 116.0, 123.0, 127.7, 132.3, 143.6, 144.5, 163.8; LC-MS, MS m/z 219 (M+H); *Anal*. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83. Found: C, 65.97; H, 6.46; N, 12.74.

(E)-3-(Isopropoxyimino)-1-methylindolin-2-one ((E)-6ad) and (E)-N-(1-methyl-2-oxoindolin-3-ylidene)propan-2-amine oxide ((E)-7ad). To a solution of isatin oxime 5a (1.01 g, 5.73 mmol) in DMF (23 mL, 0.25*M*) was added NaH (60% 0.275 g of a dispersion in oil, 6.88 mmol) followed after 10 min by 2-iodopropane (1.18 g, 6.88 mmol). After stirring the brown reaction mixture at rt for 15 h, the DMF was removed *in vacuo*, the residue dissolved in EtOAc (150 mL), and then washed with 1*N* HCl (2 × 50 mL). The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers washed with brine, dried, and concentrated to afford viscous brown oil. Chromatography on a column of silica gel using a 3:1 mixture of hexane and EtOAc as eluant gave nitrone *(E)*-**7ad** (0.675 g, 54% yield) as an orange solid followed by oxime ether *(E)*-**6ad** (0.441 g, 45% yield) as a viscous yellow oil which solidified upon standing at rt.

(*E*)-7ad: m.p. 113.0–114.5°C; IR (neat) νmax 3055, 2982, 1701, 1610, 1551, 1466, 1241, 737 cm^{-1}; ^{1}H NMR δ 1.45 (dd, J = 6.56, 1.37 Hz, 6H), 3.27 (d, J = 1.22 Hz, 3 H), 6.28–6.37 (m, 1H), 6.82 (d, J = 7.93 Hz, 1H), 7.07–7.12 (m, 1H), 8.37 (d, J = 7.63 Hz, 2H); ^{13}C NMR δ 20.5, 26.2, 61.9, 107.7, 118.5, 123.2, 124.8, 131.2, 133.1, 140.9, 160.6. LC-MS, MS m/z 219 (M+H); *Anal*. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83; found: C, 66.17; H, 6.24; N, 12.69.

(*E*)-6ad: m.p. 68.5–72.0°C; IR (neat) νmax 3057, 2976, 1727, 1608, 1468, 1330, 971, 748 cm^{-1}; ^{1}H NMR δ 1.41 (dd, J = 6.41, 1.53 Hz, 6H), 3.21 (d, J = 1.53 Hz, 3H), 4.69–4.80 (m, 1H), 6.79 (d, J = 7.93 Hz, 1H), 7.03 (t, J = 7.48 Hz, 1H), 7.32–7.38 (m, 1H), 7.93 (d, J = 7.32 Hz, 1H); ^{13}C NMR δ 21.8, 26.1, 79.6, 108.3, 116.0, 122.9, 127.7, 132.2, 143.3, 144.4, 163.8; LC-MS, MS m/z 219 (M+H); *Anal*. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83; found: C, 66.03; H, 6.24; N, 12.80.

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)pentan-3-amine oxide ((E)-7ae). This compound was obtained as orange solid, m.p. 82.5–84.0°C; ^{1}H NMR δ 0.89 (t, J = 7.48 Hz, 6 H), 1.64–1.77 (m, 2 H), 1.92–2.05 (m, 2 H), 3.28 (s, 3 H), 6.06–6.14 (m, 1 H), 6.83 (d, J = 7.93 Hz, 1 H), 7.10 (dt, J = 7.63, 0.92 Hz, 1 H), 7.37 (dt, J = 7.78, 1.22 Hz, 1 H), 8.42 (d, J = 6.71 Hz, 1 H); ^{13}C NMR δ 10.4, 26.2, 26.6, 73.0, 107.7, 118.2, 123.2, 124.9, 131.4, 135.4, 140.8, 160.8; LC-MS, MS m/z 247 (M+H); *Anal*. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.36; N, 11.37. Found: C, 68.18; H, 7.13; N, 11.38.

(E)-1-methyl-3-(pentan-3-yloxyimino)indolin-2-one ((E)-6ae). This compound was obtained as yellow viscous oil, ^{1}H NMR δ 0.96 (t, J = 7.32 Hz, 6 H), 1.69–1.85 (m, 4 H), 3.23 (s, 3 H), 4.38–4.45 (m, 1 H), 6.81 (d, J = 7.93 Hz, 1 H), 7.05 (dt, J = 7.48, 0.92 Hz, 1 H), 7.36 (dt, J = 7.78, 1.22 Hz, 1 H), 7.94 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 9.6, 26.2, 89.8, 108.3, 116.1, 123.0, 127.6, 132.1, 143.4, 144.3, 163.9; LC-MS, MS m/z 247 (M+H).

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)cyclopentanamine oxide ((E)-7af). This compound was obtained as orange solid, m.p. 98.0–100.0°C; ^{1}H NMR δ 1.64–1.73 (m, 2 H) 1.88–1.98 (m, 2 H), 2.02–2.09 (m, 2 H), 2.10–2.19 (m, 2 H), 3.27 (s, 3 H), 6.45–6.53 (m, 1 H), 6.81 (d, J = 7.93 Hz, 1 H), 7.08 (dt, J = 7.63, 0.92 Hz, 1 H), 7.35 (dt, J = 7.78, 1.22 Hz, 1 H), 8.35 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 26.1, 26.1, 31.8, 70.7, 107.7, 118.5, 123.2, 124.8, 131.2, 133.8, 140.8, 160.7; LC-MS, MS m/z 245 (M+H); *Anal*. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.46. Found: C, 68.95; H, 6.56; N, 11.44.

(E)-3-(cyclopentyloxyimino)-1-methylindolin-2-one ((E)-6af). This compound was obtained as yellow solid, m.p. 54.0–55.5°C; ^{1}H NMR δ 1.59–1.68 (m, 2 H), 1.70–1.81 (m, 2 H), 1.87–1.96 (m, 2 H), 1.97–2.05 (m, 2 H), 3.21 (s, 3 H), 5.06–5.12 (m, 1 H), 6.79 (d, J = 7.93 Hz, 1 H), 7.03 (dt, J = 7.55, 0.76 Hz, 1 H), 7.35 (dt, J = 7.78, 1.22 Hz, 1 H), 7.88 (d, J = 7.32 Hz, 1 H); ^{13}C NMR δ 23.9, 25.9, 32.6, 89.2, 108.4, 116.0, 123.0, 127.5, 132.3, 143.6, 144.4, 163.8; LC-MS, MS m/z 245 (M+H); *Anal*. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.46. Found: C, 69.01; H, 6.52; N, 11.47.

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)cyclohexanamine oxide ((E)-7ag). This compound was obtained as orange solid, m.p. 109.5–110.5°C; ^{1}H NMR δ 1.19–1.30 (m, 1 H), 1.40–1.54 (m, 2 H), 1.68–1.75 (m, 1 H), 1.86–1.98 (m, 6 H), 3.27 (s, 3 H), 5.94–6.02 (m, 1 H), 6.81 (d, J = 7.63 Hz, 1 H), 7.08 (dt, J = 7.63, 0.92 Hz, 1 H), 7.35 (dt, J = 7.71, 1.37 Hz, 1 H), 8.36 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 25.1, 25.2, 26.1, 30.8, 69.6, 107.7, 118.5, 123.2, 124.8, 131.2, 133.2, 140.8, 160.6; LC-MS, MS m/z 249 (M+H); *Anal*. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.77; H, 7.00; N, 10.82.

(E)-3-(cyclohexyloxyimino)-1-methylindolin-2-one ((E)-6ag). This compound was obtained as yellow solid, m.p. 57.0–60.0°C; ^{1}H NMR δ 1.30–1.46 (m, 3 H), 1.53–1.59 (m, 1 H), 1.61–1.70 (m, 2 H), 1.72–1.82 (m, 2 H), 2.03–2.11 (m, 2 H), 3.23 (s, 3 H), 4.48–4.57 (m, 1 H), 6.80 (d, J = 7.63 Hz, 1 H), 7.03–7.07 (m, 1 H), 7.36 (dt, J = 7.78, 1.22 Hz, 1 H), 7.95 (d, J = 7.32 Hz, 1 H); ^{13}C NMR δ 23.6, 25.6, 26.2, 31.7, 84.4, 108.3, 116.1, 123.0, 127.7, 132.2, 143.5, 144.4, 163.9; LC-MS, MS m/z 249 (M+H); *Anal*. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.75; H, 6.96; N, 10.79.

(E)-1-(4-methoxyphenyl)-N-(1-methyl-2-oxoindolin-3-ylidene)methanamine oxide ((E)-7ah). This compound was obtained as orange solid, m.p. 126.0–133.0°C; ^{1}H NMR δ 3.29 (s, 3 H), 3.78 (s, 3 H), 5.88 (s, 2 H), 6.80 (d, J = 7.63 Hz, 1 H), 6.87 (d, J = 8.85 Hz, 2 H), 7.06 (t, J = 7.78 Hz, 1 H), 7.35 (dt, J = 7.71, 1.07 Hz, 1 H), 7.55 (d, J = 8.55 Hz, 2 H), 8.30 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 26.3, 55.4, 65.3, 107.8, 114.2, 118.3, 123.2, 125.0, 126.3, 131.2, 131.5, 133.4, 141.1, 160.2, 160.8; LC-MS, MS m/z 297 (M+H); *Anal*. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.69; H, 5.42; N, 9.24.

(E)-3-(4-methoxybenzyloxyimino)-1-methylindolin-2-one ((E)-6ah). This compound was obtained as orange solid, m.p. 96.5–101.0°C; ^{1}H NMR δ 3.23 (s, 3 H), 3.81 (s, 3 H), 5.44 (s, 2 H), 6.80 (d, J = 7.94 Hz, 1 H), 6.91 (d, J = 8.55 Hz, 2 H), 7.00 (t, J = 7.63 Hz, 1 H), 7.35 (dt, J = 7.86, 1.07 Hz, 1 H), 7.39 (d, J = 8.54 Hz, 2 H), 7.88 (d, J = 7.32 Hz, 1 H); ^{13}C NMR δ 26.2, 55.4, 79.2, 108.3, 114.1, 116.0, 123.0, 128.0,

128.5, 130.3, 132.5, 144.0, 144.6, 160.0, 163.7; LC-MS, MS m/z 297 (M+H)); *Anal*. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.63; H, 5.31; N, 9.18.

(E)-2-tert-butoxy-N-(1-methyl-2-oxoindolin-3-ylidene)-2-oxoethanamine oxide ((E)-7ai). This compound was obtained as orange solid, m.p. 132.0–142.0°C; ^{1}H NMR δ 1.50 (s, 9 H), 3.25 (s, 3 H), 5.45 (s, 2 H), 6.83 (d, J = 7.93 Hz, 1 H), 7.10 (t, J = 7.63 Hz, 1 H), 7.39 (dt, J = 7.78, 1.22 Hz, 1 H), 8.34 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 26.2, 28.1, 65.4, 83.7, 107.9, 117.8, 123.3, 125.3, 132.0, 134.9, 141.6, 160.7, 164.3; LC-MS, MS m/z 313 (M+Na); *Anal*. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.24; N, 9.65. Found: C, 61.72; H, 6.50; N, 9.28.

(E)-tert-butyl-2-(1-methyl-2-oxoindolin-3-ylideneaminooxy) acetate ((E)-6ai). This compound was obtained as yellow solid, m.p. 120.5–122.0°C; ^{1}H NMR δ 1.48 (s, 9 H), 3.22 (s, 3 H), 4.90 (s, 2 H), 6.81 (d, J = 7.63 Hz, 1 H), 7.06 (dt, J = 7.63, 0.92 Hz, 1 H), 7.39 (dt, J = 7.78, 1.22 Hz, 1 H), 8.05 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 26.2, 28.3, 73.3, 82.5, 108.5, 115.7, 123.3, 128.7, 133.0, 144.8, 145.1, 163.5, 167.7; LC-MS, MS m/z 313 (M+Na); *Anal*. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.24; N, 9.65. Found: C, 61.87; H, 6.525; N, 9.56.

(E)-3-(Isopropoxyimino)-1-methylindolin-2-one ((E)-6ad). To a slurry of **4a** (5.02 g, 6.14 mmol) in EtOH (12 mL) was added a brown cloudy solution of 2-(ammoniooxy)propane chloride (0.822 g, 7.37 mmol) in H_2O (4 mL). The resulting brown reaction mixture was stirred at rt for 3 h, the solvent was removed *in vacuo* to leave a greenish-yellow oil which was redissolved in EtOAc (50 mL), and washed with 1*N* aqueous HCl (2 × 10 mL). The aqueous layers were extracted with EtOAc (50 mL), and the organic layers combined and washed with 10% aqueous Na_2CO_3 (10 mL) and brine before being dried and concentrated to afford a viscous yellow oil. ^{1}H NMR δ 1.42 (d, J = 6.10 Hz, 6H), 3.23 (s, 3H), 4.73–4.81 (m, 1H), 6.81 (d, J = 7.93 Hz, 1H), 7.05 (t, J = 7.63 Hz, 1H), 7.37 (t, J = 7.32 Hz, 1H), 7.95 (d, J = 7.63 Hz, 1H); ^{13}C NMR δ 21.8, 26.1, 79.6, 108.3, 116.1, 122.9, 127.7, 131.7, 143.3, 144.4, 163.9; LC-MS, MS m/z 219 (M+H).

3-(Hydroxyimino)-1-phenylindolin-2-one (5b). 3-(Hydroxyimino)-1-phenylindolin-2-one (**5b**) was prepared in quantitative yield from 1-phenylisatin (**4b**) according to the procedure described for the preparation of **5a**. This compound was obtained as orange solid, m.p. 219.0–221.0°C (lit. m.p. 221°C) [26]; ^{1}H NMR δ 6.79 (d, J = 7.9 Hz, 1 H), 7.14 (dt, J = 7.6, 0.6 Hz, 1 H), 7.35 (dt, J = 7.8, 1.2 Hz, 1 H), 7.41–7.44 (m, 2 H), 7.46 (t, J = 7.6 Hz, 1 H), 7.57 (t, J = 7.6 Hz, 2 H), 8.15 (d, J = 7.6 Hz, 1 H); ^{13}C NMR δ 109.8, 116.2, 123.7, 127.0, 127.8, 128.7, 129.8, 132.1, 134.2, 144.0, 144.3, 164.5; *Anal*. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.75; found: C, 70.45; H, 4.14; N, 11.49.

(E)-3-(Isopropoxyimino)-1-phenylindolin-2-one ((E)-6bd) and (E)-N-(2-oxo-1-phenylindolin-3-ylidene)propan-2-amine oxide ((E)-7bd). Compounds ***(E)*-6bd** and ***(E)*-7bd** were prepared from **5b** in 36% and 47% yield, respectively, following the alkylation procedure used for the preparation of *(E)*-**6ad** and *(E)*-**7ad**.

(*E*)-7bd: This compound was obtained as orange solid, m.p. 83.0–89.0°C; ^{1}H NMR δ 1.47 (d, J = 6.4 Hz, 6 H), 6.30–6.39 (m, 1 H), 6.79 (d, J = 7.9 Hz, 1 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.8 Hz, 1 H), 7.42 (d, J = 7.0 Hz, 3 H), 7.52 (t, J = 7.5 Hz, 2 H), 8.47 (d, J = 7.3 Hz, 1 H); ^{13}C NMR δ 20.5, 62.2, 109.1, 118.7, 123.6, 124.9, 127.0, 128.4, 129.7, 131.2, 132.8, 134.1, 140.8, 160.0; LC-MS, MS m/z 281 (M+H); *Anal*. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.72; H, 5.65; N, 9.92.

(*E*)-6bd: This compound was obtained as yellow solid, m.p. 125.5–127.0°C; ^{1}H NMR δ 1.47 (d, J = 6.1 Hz, 6 H), 4.78–4.87 (m, 1 H), 6.81 (d, J = 7.9 Hz, 1 H), 7.10 (t, J = 7.5 Hz, 1 H), 7.30 (dt, J = 7.9, 1.2 Hz, 1 H), 7.41 (d, J = 7.0 Hz, 3 H), 7.52 (t, J = 7.5 Hz, 2 H), 8.05 (d, J = 6.4 Hz, 1 H); ^{13}C NMR δ 21.9, 79.9, 109.7, 116.2, 123.4, 126.8, 127.9, 128.3, 129.8, 132.1, 134.0, 143.1, 144.4, 163.0; LC-MS, MS m/z 281 (M+H); *Anal*. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.77; H, 5.72; N, 9.93.

(E)-3-(Isopropoxyimino)-1-phenylindolin-2-one ((E)-6bd) and (E)-N-(2-oxo-1-phenylindolin-3-ylidene)propan-2-amine oxide ((E)-7bd). To a solution of **5b** (104 mg, 0.437 mmol), 2-propanol (67.4 μL, 0.875 mmol) and triphenylphosphine (229 mg, 0.875 mmol) in THF (1.8 mL) maintained at 0°C was added diisopropyl azodicarboxylate (172 μL, 0.875 mmol). The resulting greenish-yellow solution was stirred at rt for 18 h, diluted with EtOAc (25 mL) and washed with aqueous 10% Na_2CO_3. The aqueous layer was extracted with EtOAc (25 mL), and the combined organic layers washed with 0.1*N* HCl (5 mL) and brine, dried and concentrated to afford a light orange viscous oil. Chromatography on a column of silica gel using a 4:1 mixture of hexane and EtOAc as eluant gave nitrone *(E)*-**7bd** (91 mg, 74% yield) as an orange solid followed by oxime ether *(E)*-**6bd** (12.3 mg, 10% yield) as a yellow viscous oil which solidified upon standing at rt.

(*E*)-7bd: ^{1}H NMR δ 1.48 (d, J = 6.4 Hz, 6 H), 6.30–6.39 (m, 1 H), 6.80 (d, J = 7.9 Hz, 1 H), 7.13 (t, J = 7.6 Hz, 1 H), 7.29 (dt, J = 7.8, 0.9 Hz, 1 H), 7.41–7.46 (m, 3 H), 7.54 (t, J = 7.5 Hz, 2 H), 8.48 (d, J = 7.3 Hz, 1 H).

(*E*)-6bd: ^{1}H NMR δ 1.46 (d, J = 6.4 Hz, 6 H), 4.78–4.87 (m, 1 H), 6.81 (d, J = 7.9 Hz, 1 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.30 (t, J = 7.8 Hz, 1 H), 7.39–7.43 (m, 3 H), 7.52 (t, J = 7.5 Hz, 2 H), 8.05 (d, J = 7.6 Hz, 1 H).

4-Bromo-1-methylindoline-2,3-dione (4c). K_2CO_3 (4.95 g, 35.84 mmol) and CH_3I (10.17 g, 71.67 mmol) were added to a solution of 4-bromoisatin (5.4 g, 23.89 mmol) in DMF (50 mL) and the mixture heated at 80°C for 30 min. After cooling to rt, the mixture was diluted with H_2O (50 mL) and the precipitated red solid collected by filtration and washed with H_2O (2 × 25 mL). The product was dried in a vacuum oven to give **4c** (5.20 g) as a red solid that was used further without purification, m.p.199.5–200.5°C; ^{1}H NMR δ 3.25 (s, 3 H), 6.84 (d, J = 7.9 Hz, 1 H), 7.26 (d, J = 3.4 Hz, 1 H), 7.41 (t, J = 8.1 Hz, 1 H); ^{13}C NMR δ 26.4, 108.7, 116.4, 121.7, 128.6, 138.4, 153.1, 157.4, 180.7; *Anal*. Calcd for $C_9H_6BrNO_2$: C, 45.03; H, 2.51; N, 5.83; Br, 33.28. Found: C, 44.84; H, 2.48; N, 5.83; Br, 33.02.

4-Bromo-3-(hydroxyimino)-1-methylindolin-2-one (5c). Compound **5c** was prepared from **4c** using the procedure described for the preparation of **5a** with the exception that the reaction was heated at 55°C overnight. This compound was obtained as orange solid, m.p. 186.0–188.5°C; ^{1}H NMR δ 3.25 (s, 3 H), 6.84 (d, J = 7.9 Hz, 1 H), 7.25 (d, J = 7.2 Hz, 1 H), 7.41 (t, J = 7.9 Hz, 1 H); ^{13}C NMR δ 26.4, 108.7, 116.4, 121.7, 128.6, 138.4, 153.1, 157.4, 180.7; *Anal*. Calcd for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.76; N, 10.98; Br, 31.32. Found: C, 42.14; H, 2.73; N, 10.74; Br, 30.95.

(Z)-4-Bromo-3-(isopropoxyimino)-1-methylindolin-2-one ((Z)-6cd) and (E)-4-bromo-3-(isopropoxyimino)-1-methylindolin-2-one ((E)-6cd). To a slurry of **4c** (1.03 g, 4.29 mmol) in EtOH (12 mL) was added a brown cloudy solution of 2-(ammoniooxy)propane chloride (0.527 g, 4.72 mmol) in H_2O (4 mL). The brown mixture was stirred at 52°C for 3.5 h, the solvent removed in *vacuo* and the residue dissolved in EtOAc (50 mL) and washed with H_2O (50 mL). The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers were washed with brine, dried, and concentrated to leave a light orange viscous oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (3:1 then 2:1) as eluant afforded oxime ether (*Z*)-**6cd** (0.706 g, 56% yield) followed by oxime ether *(E)*-**6cd** (0.448 g, 35% yield) both isolated as yellow solids.

(Z)-6cd: m.p. 67.0–68.5°C; ^{1}H NMR δ 1.46 (d, J = 6.41 Hz, 6H), 3.20 (s, 3H), 4.70–4.78 (m, 1H), 6.74 (d, J = 7.93 Hz, 1H), 7.15 (t, J = 7.93 Hz, 1H), 7.22 (d, J = 8.24 Hz, 1H); ^{13}C NMR δ 21.4, 25.8, 80.1, 107.0, 116.7, 118.5, 127.6, 131.0, 141.1, 144.9, 156.6; LC-MS, MS m/z 297 (M+H); *Anal*. Calcd for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; N, 9.42; Br, 26.89. Found: C, 48.74; H, 4.28; N, 9.32; Br, 27.00.

***(E)*-6cd**: m.p. 78.0–79.5°C; ^{1}H NMR δ 1.44 (d, J = 6.10 Hz, 6H), 3.22 (s, 3H), 4.76–4.85 (m, 1H), 6.74 (d, J = 7.93 Hz, 1H), 7.16 (t, J = 8.09 Hz, 1H), 7.28 (dd, J = 8.24, 0.92 Hz, 1H); ^{13}C NMR δ 21.8, 26.4, 81.0, 107.4, 117.6, 119.8, 129.3, 132.6, 139.7, 147.1, 163.5; LC-MS, MS m/z 297 (M+H).

(*Z*)-**6cd** was also prepared exclusively by alkylation of **5c** with 2-iodopropane or 2-bromopropane under the same conditions used to prepare *(E)*-**6ad**, m.p. 66.5–68.0°C; ^{1}H NMR δ 1.46 (d, J = 6.4 Hz, 6H), 3.20 (s, 3H), 4.69–4.78 (m, 1H), 6.74 (dd, J = 7.6, 0.6 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.23 (dd, J = 8.2, 0.6 Hz, 1H); LC-MS, MS m/z 297 (M+H).

(*Z*)-**6cd** was also prepared exclusively in 85% yield from **5c** and isopropyl alcohol under the Mitsunobu conditions described for the preparation of *(E)*-**6bd** and *(E)*-**7bd** above. This compound was obtained as yellow solid, m.p. 66.0–67.5°C; ^{1}H NMR δ 1.47 (d, J = 6.4 Hz, 6H), 3.21 (s, 3H), 4.70–4.79 (m, 1H), 6.75 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H); LC-MS, MS m/z 297 (M+H).

X-ray crystallographic data for compounds *(E)*-**6bd** and *(E)*-**7ad** have also been deposited with the Cambridge Crystallographic Data Center as CCDC 661142 and CCDC 661143, respectively.

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