calcd for $C_{12}H_{11}F_3O_3S$ 292.0381, found 292.0381.

Preparation of Trifluoroacetate 7. A solution of 302 mg of methyl 2-hydroxy-2-phenylpropionate (atrolactic acid methyl ester) and 265 mg of 2,6-lutidine in 6 mL of ether was cooled to 0 °C, and 493 mg of trifluoroacetic anhydride was added dropwise. After 10 min at 0 °C water was added to the stirred solution. A rapid aqueous workup followed using consecutive washings with cold HCl, $NaHCO_3$, and saturated NaCl solutions. The ether extract was dried over $MgSO_4$ and filtered, and the solvent was removed using a rotary evaporator. The residue was distilled to give 420 mg (91%) of the trifluoroacetate 7, bp 50 °C (0.05 mm): ^1H NMR ($CDCl_3$) δ 7.55–7.48 (m, 2 H), 7.45–7.33 (m, 3 H), 3.732 (s, 3 H), 2.076 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.32, 156.07 (q, J_{C-F} = 43 Hz), 137.71, 129.09, 128.91, 124.75, 114.49 (q, J_{C-F} = 286 Hz), 85.75, 53.27, 23.21. Anal. Calcd for $C_{12}H_{11}F_3O_4$: C, 52.18; H, 4.01. Found: C, 52.40; H, 4.26.

Kinetics Procedures. Before beginning a kinetic run, the spectrometer was shimmed using a $CDCl_3$ sample of the same volume as the kinetics sample. Approximately 5–10 mg of the appropriate trifluoroacetate was dissolved per 1 mL of the given solvent, and part of the solution was placed in an NMR tube. For runs at 25 °C, the tube was placed in the NMR probe held at 25.0 ● 0.2 °C. The sample was allowed to thermally equilibrate for 3 min, and ^{19}F spectra were recorded periodically. Spectra were recorded in the unlocked mode with a 4-s delay between pulses. For substrates that react at elevated temperatures, the NMR tube was sealed and the tube was placed in a constant temperature bath at the appropriate temperature for certain time periods. The tube was then withdrawn, quenched in cold water, and analyzed by ^{19}F NMR (unlocked) at room temperature (where the reaction proceeds at a negligible rate). The reactions were monitored over approximately 2 half lives. First-order rate constants were calculated by standard least-squares procedures. Correlation coefficients were all greater than 0.9996. Maximum standard deviations in duplicate runs were ±2%.

Acknowledgment is made to the National Science Foundation for support of this research.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for 2 and 6 (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

Regioselective Alkylation of Phenoxy-Substituted 3-(Methylthio)indolin-2(3*H*)-ones. Preparation of 3-, 1,3-, and 1,3,3-Substituted Indolin-2(3*H*)-ones

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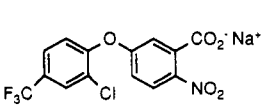
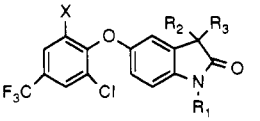
Diphenyl ethers are an important class of herbicides and thus have attracted considerable attention in the agricultural chemical community. They act as contact herbicides, causing chlorosis and tissue necrosis.[1] Recent mechanistic elucidation of acifluorfen, 1, a typical diphenyl ether herbicide, has determined the site of action to be the enzyme protoporphyrinogen oxidase.[2] Inhibition of this enzyme causes protoporphyrin IX buildup which leads to singlet oxygen formation and ultimate membrane damage.



1



2

X = H, halogen
R_1, R_2, R_3 = H, alkyl

In connection with a synthesis program directed toward diphenyl ethers containing the indolin-2(3*H*)-one (oxindole) moiety 2,[3,4] we required an efficient route to a variety of functionalized indolin-2-ones in an effort to fully explore their herbicidal activity. Two major structural variations were chosen for study: substitution patterns in the lactam ring (mono-, di-, and trisubstitution) and isomeric substitution of the phenoxy group in the benzenoid ring.

The literature is replete with methods for the preparation of indolin-2-ones.[5] Several classical approaches have been used including reduction of the corresponding isatins,[6] modification of the Fisher indole synthesis via oxidation of methyleneindoline intermediates,[7,8] reduction of *o*-nitrophenylacetic acid derivatives,[9] as well as others.[9d,10,11] Major drawbacks of many of these approaches include the harsh reaction conditions as well as the availability of the starting materials needed for the substitution patterns in the final products. More recent approaches include radical cyclizations[12,13] of substituted acetanilides, hypohalite degradation of homophthalimides,[14] Pummerer rearrangements,[15] and carbenoid insertions of β-diazoacetanilides.[16] Most of these approaches require N-substitu-

(1) Ashton, F. M.; Crafts, A. S. *Mode of Action of Herbicides*, 2nd ed.; Wiley: New York, 1981; pp 224–235.

(2) For recent studies on the mechanism of action of acifluorfen-methyl see: (a) Matringe, M.; Camadro, J.-M.; Labbe, P.; Scalla, R. *Biochem. J.* **1989**, *260*, 231. (b) Witkowski, D.; Halling, B. *Plant. Physiol.* **1989**, *90*, 1239.

(3) Neilsen, D. R. U.S. Patent 4 571 255, 1986.

(4) (a) Hunt, D. A.; Schwindeman, J. A. U.S. Patent 4 911 754, 1990. (b) Neilsen, D. R. Eur. Pat. Appl. EP 238 266, 1987; *Chem. Abstr.* **1988**, *108*, 37823v. (c) Camilleri, P.; Gray, A.; Weaver, K.; Bowyer, J.; Williams, D. *J. Agric. Food Chem.* **1989**, *37*, 519.

(5) Several classical methods for the preparation of indolin-2-ones are presented in (a) Julian, P. L.; Meyer, E. M.; Printy, H. C. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; Wiley: New York, 1952; Vol. 3, Chapter 1. (b) Sundberg, R. J. In *The Chemistry of Indoles*; Blomquist, A. T., Ed.; Monograph 18; Academic Press: New York, 1970; pp 357–364.

(6) Baeyer, A.; Knop, C. *Liebigs Ann. Chem.* **1866**, *140*, 1. For a recent utilization of this method, see: Pavia, M. R.; Moos, W. H.; Hershenson, F. M. *J. Org. Chem.* **1990**, *55*, 560.

(7) Plancher, G. *Chem. Ber.* **1898**, *31*, 1488.

(8) (a) Boyd-Barrett, H.; Robinson, R. *J. Chem. Soc.* **1932**, 317. (b) King, F.; Robinson, R. *J. Chem. Soc.* **1932**, 326. See ref 4a for a recent utilization of this approach in the construction of 1,3,3-trialkylindolin-2-ones.

(9) (a) Baeyer, A. *Chem. Ber.* **1878**, *11*, 582. (b) Reissert, A. *Chem. Ber.* **1897**, *30*, 1030. For more recent examples, see: (c) Mertens, A.; Muller-Beckmann, B.; Kampe, W.; Holck, J.-P.; von der Saal, W. *J. Med. Chem.* **1987**, *30*, 1279. (d) Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968**, *24*, 6093.

(10) For cyclization of *N*-acylphenylhydrazines see: (a) Brunner, K. *Monatsh.* **1896**, *17*, 479. (b) Brunner, K. *Monatsh.* **1897**, *18*, 95.

(11) For Lewis acid catalyzed cyclizations of α-haloacetanilides, see: (a) Stolle, R. *Chem. Ber.* **1914**, *47*, 2120. More recent applications include: (b) Beer, R. J.; Davenport, H. F.; Robertson, A. *J. Chem. Soc.* **1953**, 1262. For a related approach, see: (c) Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1981**, *29*, 128.

(12) For photoinduced cyclizations of mono- and dianions of *N*-acyl-*o*-chloroanilines, see: Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435.

(13) For a radical cyclization of *N*-methyl-*N*-acryloylanilide in the synthesis of geneserine, see: Wright, C.; Shulkind, M.; Jones, K.; Thompson, M. *Tetrahedron Lett.* **1987**, *28*, 6389.

(14) Jonsson, N. A.; Moses, P. *Acta Chem. Scand., Ser. B* **1974**, *28*, 225.

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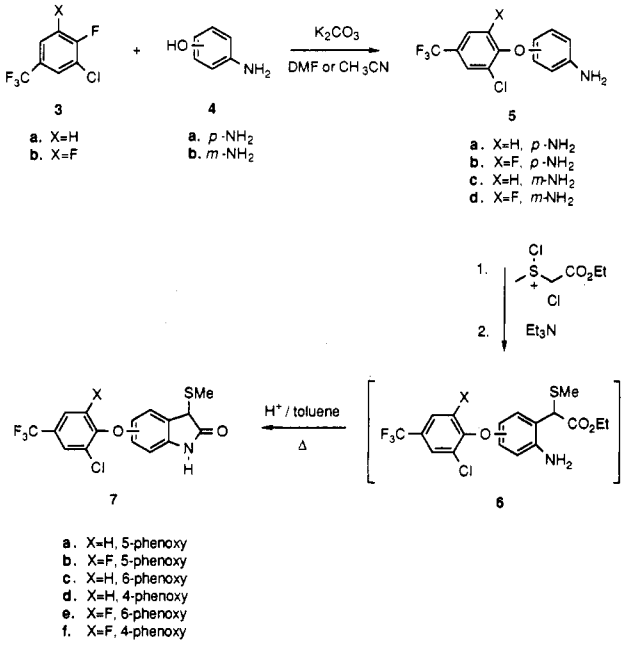
Scheme I. Synthesis of 4-, 5-, and 6-Phenoxyindolin-2-ones



tion as a prerequisite. Another approach which has gained wide acceptance is the method developed by Gassman.[17,18] This approach allows the conversion of anilines to 3-(methylthio)indolin-2-ones via a Sommelet-Hauser type rearrangement of intermediate azasulfonium salts. The reaction takes place under mild conditions and can be run with both N-substituted and unsubstituted anilines. The 3-methylthio group can then be removed reductively. It was realized that the 3-methylthio group could potentially act as an activating/blocking group for any subsequent alkylation reactions.

The selective alkylation of indolin-2-ones has been extensively studied in the past. Early reports on the alkylation of 1,3,3-unsubstituted indolin-2-ones generally found poor selectivity regardless of the conditions employed.[19] Attempted selective mono C-3 alkylation of *N*-methylindolin-2-ones were equally discouraging.[20] Other less direct methods have been described for the preparation of mono C-3 alkylated compounds. Alkylation at C-3 of 3-acetylindolin-2-one followed by deacetylation affords 3-alkylindolin-2-ones.[21] Reduction of 3-alkylideneindolin-2-ones, prepared by the condensation of 3-unsubstituted indolin-2-ones with aldehydes and ketones, also gives mono C-3 alkylated products.[20a,22] Selective C-3 alkylation has also been carried out by prior N-acetylation.[23] Deacetylation readily affords 3,3-dialkylated products. One limitation of this approach is the inability to prepare unsymmetrically alkylated products. Kende[24] has reported the regioselective C-3 alkylation of the dianion of oxindole using two equivalents each of *n*-butyllithium and TMEDA. While this approach worked well enough in the absence of other functionality, the strongly basic conditions might be incompatible with sensitive groups.

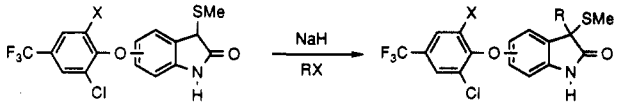
Herein is described the mild and regiospecific alkylation of 3-(methylthio)indolin-2-ones, obtained via the Gassman oxindole synthesis, with a wide variety of substrates. Using this approach, 3-, 1,3-, and 1,3,3-substituted indolin-2-ones can be prepared efficiently.

Table I. Synthesis of Indolin-2-ones 7 from Anilines 5 and Ethyl (Methylthio)acetate

aniline	X	phenoxy position	indolin-2-one	phenoxy position	yield,[a] %
5a	H	para	**7a**	5	49
5b	F	para	**7b**	5	43
5c	H	meta	**7c**	6	40
			7d	4	17
5d	F	meta	**7e**	6	36
			7f	4	14

[a] Yields refer to isolated yields by flash chromatography.

Table II. C-3 Alkylation of 3-(Methylthio)indolin-2-ones



compd	X	phenoxy position	R	product	yield,[a] %
7a	H	5	Me	**8a**	60
7b	F	5	Me	**8b**	69
7c	H	6	Me	**8c**	77
7d	H	4	Me	**8d**	50
7a	H	5	*i*-Pr	**8e**	26[b]
7a	H	5	CH_2Ph	**8f**	78
7a	H	5	CH_2CO_2Et	**8g**	81
7a	H	5	$CH(CH_3)CO_2Et$	**8h**	15[c]
				8i	14[c]

[a] Yields refer to isolated yields by flash chromatography. [b] In addition, 8% of O-alkylated compound **11** was isolated (see text). [c] This represents the isolated yield for the two diastereomeric C-alkylated products obtained. In addition, 32% of O-alkylated compound **12** was isolated (see text).

Results and Discussion

Synthesis of Phenoxy-Substituted 3-(Methylthio)-indolin-2-ones. The desired phenoxy-substituted indolin-2-ones **7a–f** were easily prepared in two steps (Scheme I). Coupling between *p*- and *m*-aminophenol and pentafluorotoluene **3b** was carried out in CH_3CN at reflux. The less reactive tetrafluorotoluene **3a** needed more forcing conditions (DMF, 100 °C). Cyclization of the phenoxyanilines **5a–d** to the regioisomeric indolin-2-ones **7a–f** was accomplished by minor modification of the method reported by Gassman.[17b] The two symmetrical 4-phenoxy-

(16) (a) Etkin, N.; Babu, S.; Fooks, C.; Durst, T. *J. Org. Chem.* **1990**, *55*, 1093. (b) Doyle, M. P.; Shanklyn, M.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017.

(17) (a) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5508. (b) Gassman, P. G.; Greutzmacher, G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5512. (c) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 2718.

(18) (a) Walsh, D. A.; Moran, H. W.; Shamblee, D. A.; Welstead, W. J.; Nolan, J. C.; Sancilio, L. F.; Graff, G. *J. Med. Chem.* **1990**, *33*, 2296. (b) Raphael, R. A.; Ravenscroft, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1823. (c) Warpehoski, M. A.; Bradford, V. S. *Tetrahedron Lett.* **1986**, *27*, 2735. (d) Walsh, D. A.; Moran, H. W.; Shamblee, D. A.; Uwaydah, I. M.; Welstead, W. J.; Sancilio, L. F.; Dannenburg, W. N. *J. Med. Chem.* **1984**, *27*, 1379. (e) Gassman, P. G.; Roos, J. J.; Lee, S. L. *J. Org. Chem.* **1984**, *49*, 717. (f) Walsh, D. A.; Shamblee, D. A.; Welstead, W. J.; Sancilio, L. F. *J. Med. Chem.* **1982**, *25*, 446.

(19) (a) Gruda, I. *Can. J. Chem.* **1972**, *50*, 18. (b) Horning, D. E.; Lacasse, G.; Muchowski, J. M. *Can. J. Chem.* **1971**, *49*, 246. (c) Wenkert, E.; Blossey, E. C. *J. Org. Chem.* **1962**, *27*, 4656.

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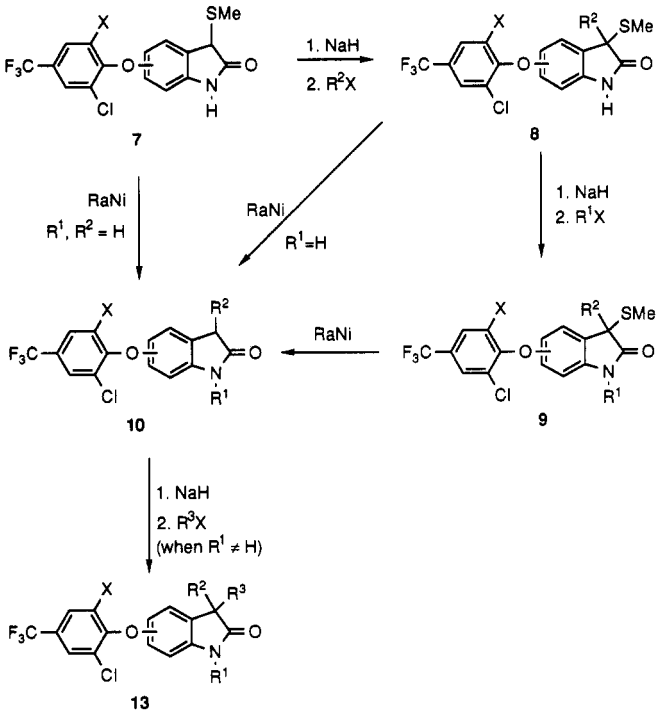
(21) Reisch, J.; Muller, M.; Labitzke, H. *Arch. Pharm.* **1984**, *317*, 639.

(22) (a) Autrey, R. L.; Tahk, F. C. *Tetrahedron* **1967**, *23*, 901. (b) Elliot, I. W.; Rivers, P. *J. Org. Chem.* **1964**, *29*, 2438. (c) Weiland, T.; Unger, O. *Chem. Ber.* **1963**, *96*, 253.

(23) (a) Robertson, D. W.; Krushinski, J. H.; Beedle, E. E.; Wyss, V.; Pollock, G. D.; Wilson, H.; Kauffman, R.; Hayes, J. S. *J. Med. Chem.* **1986**, *29*, 1832. (b) Takayama, K.; Isobe, M.; Harano, K.; Taguchi, T. *Tetrahedron Lett.* **1973**, 365.

(24) Kende, A. S.; Hodges, J. C. *Synth. Commun.* **1982**, *12*, 1.

Scheme II. Alkylation of 3-(Methylthio)indolin-2-ones



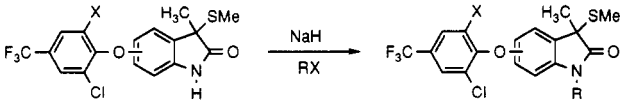
anilines **5a** and **5b** gave **7a** and **7b**, respectively, after rearrangement and intramolecular cyclization (Table I). As expected,[25] the unsymmetrical phenoxyaniline **5c** gave two products, **7c** and **7d**, arising from either of two ortho rearrangements of the intermediate azasulfonium salt. The 6-phenoxy isomer predominates due in large part to the less demanding steric requirement for rearrangement of the azasulfonium salt to the less hindered position para to the phenoxy group. In similar fashion **5d** gave rise to **7e** and **7f**. Amino esters **6** were somewhat unstable as they slowly cyclized at room temperature. The crude rearrangement products derived from **5a–d** were heated to induce rapid cyclization. Using this approach we were able to obtain the requisite 4-, 5-, and 6-phenoxyindolin-2-ones to be used in the alkylation reactions.

Alkylation Studies. Initial alkylation studies were carried out on compounds **7a** and **7b** with methyl iodide. Various conditions were examined to elicit selective alkylation. Treatment of these compounds with sodium hydride, potassium carbonate, or potassium *tert*-butoxide and methyl iodide in DMSO at room temperature gave selective C-alkylation.[26] To our knowledge, this is the first example of selective C-alkylation of a substituted 3-(methylthio)indolin-2-one.[27] A previous report[18b] described unsuccessful attempts to obtain selective C-alkylation in a similar system.

To test the general applicability of this reaction, a wide range of electrophiles were reacted with the 4-, 5-, and 6-phenoxy substituted compounds **7a–d** (Table II). Treatment of these indolin-2-ones with sodium hydride and a variety of primary alkyl halides gave exclusive C-alkylation (Scheme II). The reaction was rapid, generally being complete within 1–4 h after addition of the electrophile, and there was no evidence of competing N- or O-alkylation as judged by the chemical shifts in the ^{1}H NMR. When alkylation with branched alkyl halides was attempted, competing O-alkylation became a problem. Reaction of **7a** with 2-bromopropane gave the expected 3-isopropylindolin-2-one derivative **8e** (26%) as well as the 2-isopropoxyindole **11** (8%). The identity of **11** was established unequivocally by the presence of the downfield shift of the isopropyl methine hydrogen to 5.26 ppm in the ^{1}H NMR, the existence of the indolin-2-one N-H, and the absence of the C-3 methine of the indolin-2-one. This reaction was also rather sluggish, taking nearly 24 h to go to completion. Similarly, alkylation of **7a** with ethyl bromopropionate also gave competing C- and O-alkylated products. The reaction mixture was further complicated by the fact that two chiral centers were formed. Two diastereomeric C-alkylated products, **8h** and **8i**, were isolated (15% and 14%, respectively) along with the O-alkylated compound **12** (32%). One attempt was made to extend the selectivity of the reaction to include C-acylation as well. When acetic anhydride was used as the electrophile in the reaction with **7a**, a complex product mixture resulted.

The 3-alkyl-3-(methylthio)indolin-2-ones thus formed were then N-alkylated (Table III). The reaction was efficiently carried out under the same conditions as C-alkylation (sodium hydride and DMSO) to give the N-substituted compounds **9a–h** in moderate yields. Thus,

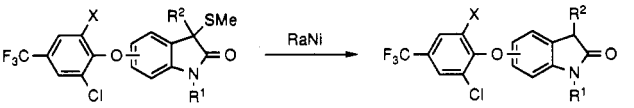
Table III. N-Alkylation of 3-Methyl-3-(methylthio)indolin-2-ones



compd	X	phenoxy position	R	product	yield,[a] %
8b	F	5	Me	**9a**	63
8c	H	6	Me	**9b**	53
8d	H	4	Me	**9c**	64
8a	H	5	$CH(CH)_3CO_2Et$	**9d**	70
8a	H	5	CH_2Ph	**9e**	62
8a	H	5	CH_2CN	**9f**	61
8a	H	5	allyl	**9g**	65
8a	H	5	propargyl	**9h**	66

[a] Yields refer to isolated yields by flash chromatography.

Table IV. Raney Nickel Desulfurization of 3-(Methylthio)indolin-2-ones



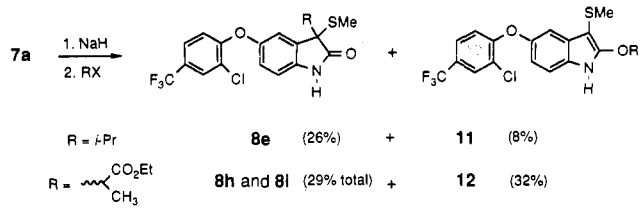
compd	X	phenoxy position	R^1	R^2	product	yield,[a] %
7b	F	5	H	H	**10a**	81
8a	H	5	H	Me	**10b**	48
8f	H	5	H	CH_2Ph	**10c**	58
9a	F	5	Me	Me	**10d**	84
9b	H	6	Me	Me	**10e**	84
9c	H	4	Me	Me	**10f**	80
9e	H	5	CH_2Ph	Me	**10g**	81
9g	H	5	allyl	Me	**10h**	73[b]
9h	H	5	propargyl	Me	**10i**	55[c]

[a] Yields refer to isolated yields by flash chromatography. [b] Raney nickel was deactivated by heating in acetone at reflux for 2 h prior to reaction. [c] Zn/AcOH was used as the reductant.

(25) A similar observation was noted with the Sommelet–Hauser type rearrangement of *m*-toluidine with β-keto sulfoxides leading to substituted 3-(methylthio)indoles. See: Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W. *J. Am. Chem. Soc.* **1974**, *96*, 5495.

(26) When either LDA or LHMDS was used to generate the enolate of **7b** in THF a complex reaction mixture was obtained.

(27) During the course of these studies, a report describing the C-3 alkylation of the related *N*-alkyl-3-(methylthio)-1,3-dihydro-2*H*-pyrrolo-[2,3-*b*]pyridin-2-one ring system appeared. See: Ting, P. C.; Kaminiski, J. J.; Sherlock, M. H.; Tom, W. C.; Lee, J. F.; Bryant, R. W.; Watnick, A. S.; McPhail, A. T. *J. Med. Chem.* **1990**, *33*, 2697.



by stepwise C- and N-alkylation, a wide variety of 1,3-dialkyl-3-(methylthio)indolin-2-ones could be prepared.

Ultimately, compounds lacking the 3-methylthio group were desired. These compounds were readily prepared by reductive desulfurization using Raney nickel[28] (Table IV). In this manner unsubstituted indolin-2-one **10a**, 3-alkylindolin-2-ones **10b–c**, and 1,3-dialkylindolin-2-ones **10d–i** were prepared in moderate to good yield. In order to avoid reduction of the *N*-allyl group during desulfurization of **9g**, the Raney nickel was deactivated by prior heating in acetone at reflux. This allowed the isolation of **10h** in 73% yield. Similar treatment of the *N*-propargyl compound **9h** failed to preserve the propargylic moiety as the only compound isolated was the partially reduced *N*-allyl compound **10h** in 34% yield. This problem was overcome by carrying out the reduction with zinc in acetic acid[15b] thereby giving compound **10i** in 55% yield.

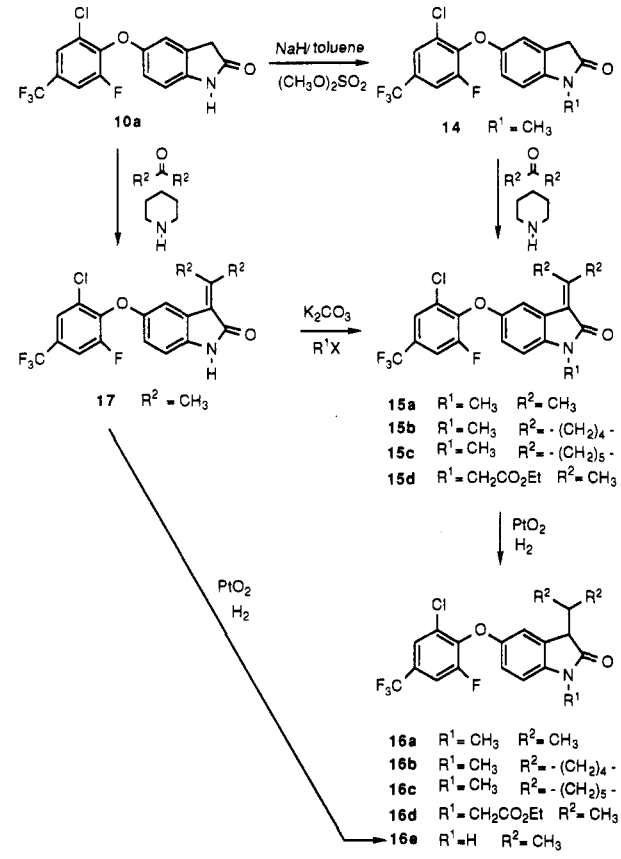
1,3,3-Trialkylindolin-2-ones could be prepared by carrying out a third alkylation on compounds such as **10d–i**. This was demonstrated by the preparation of **13** from **10d** and bromomethyl ethyl ether.

The low yields obtained for compounds **8e**, **8h**, and **8i** represent the difficulty encountered in alkylating 3-(methylthio)indolin-2-ones at C-3 with branched substituents. A more successful approach was to first convert 3-unsubstituted indolin-2-ones (e.g., **10a**) to the 3-alkylidene-substituted compounds by reaction with ketones. Reduction of the resultant carbon-carbon double bond affords 3-alkyl-substituted indolin-2-ones.[20a,22]

Although the literature reports describing the selective alkylation of unsubstituted indolin-2-ones under mild conditions were not encouraging,[19,20] we initially chose to study the feasibility of introducing N-substitution prior to alkylidine formation. Treatment of **10a** with alkyl halides under a variety of conditions led invariably to a complex mixture of products. The lone exception was the *N*-methyl analog **14**, prepared in 77% yield by treatment of **10a** with sodium hydride and dimethyl sulfate in toluene (Scheme III). Altering the above conditions gave rise to competing product formation. Since the preparation and use of other alkyl sulfates did not seem feasible, other, similar alkylating agents were examined. When methyl methanesulfonate was also found to be a selective methylating agent for **10a**, benzyl methanesulfonate was prepared[29] and used. Unfortunately, this reagent was no more selective than benzyl bromide, affording numerous products upon reaction with **10a**.

Although the N-alkylation of **10a** is limited to the preparation of the *N*-methyl compound **14**, we chose to prepare 1,3-dialkylindolin-2-ones derived via the intermediate 3-alkylidene-substituted compounds by the literature method.[20a] Treatment of **14** with a variety of ketones gave the expected alkylidenes **15a–c** in good yield. Reduction of the carbon–carbon double bond over platinum gave **16a–c** in excellent yield. Thus, the introduction

Scheme III



of branched substituents at the 3-position of indolin-2-ones has been carried out in good yield as is demonstrated by the sequence **10a** → **14** → **15** → **16**.

The limitation of the N-substitution of **10a** can be circumvented by minor modification. Since N-substitution is not a requirement for alkylidene formation, reversal of the above sequence effectively solves this problem. This was shown by the preparation of the isopropylidine compound **17** in good yield. Compound **17** does not posses any active hydrogens at C-3 to compete with N-alkylation. However, the γ-hydrogens of the alkylidene methyl groups in conjugation with both the α,β-unsaturated lactam and the benzene ring still possess sufficient reactivity. Attempted alkylation with sodium hydride and methyl iodide in DMSO gave a complex product mixture containing large amounts of polar material. Carrying out the reaction with potassium carbonate in refluxing 2-butanone gave the N-methyl compound **15a** in 69% yield using dimethyl sulfate as the alkylating agent. Preparation of **15d** using ethyl bromoacetate as the alkylating agent shows the potential for extending this reaction to alkyl halides. Reduction with platinum gave the expected product **16d** in excellent yield.

Summary

A mild and regiospecific method for the alkylation of 3-(methylthio)indolin-2-ones has been demonstrated for the introduction of alkyl groups at the 1- and 3-position of the indolin-2-one ring. Primary alkyl halides react at C-3 without any competitive N- or O-alkylation. A second alkylation occurs at N-1. Reductive desulfurization coupled with this stepwise alkylation gives 3-, 1,3-, and 1,3,3-substituted indolin-2-ones.

Reaction of 3-(methylthio)indolin-2-ones with secondary alkyl halides gives mixtures of C- and O-alkylation. This can be avoided by the preparation of 3-alkylidene-sub-

(28) Raney nickel was purchased from Aldrich Chemical Co., Inc., as an aqueous suspension (pH 9–10) and was used without any further treatment. For desulfurizations it was generally found most expedient to add the Raney nickel in small portions every 10–15 min until starting material was consumed.

(29) Crossland, R.; Servis, K. *J. Org. Chem.* **1970**, *35*, 3195.

stituted indolin-2-ones. N-Alkylation followed by reduction of the alkylidene double bond gives the desired 3- or 1,3-substituted indolin-2-ones without competitive O-alkylation.

Experimental Section

General. All reactions requiring anhydrous conditions were carried out under an atmosphere of N_2. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Dichloromethane (CH_2Cl_2), dimethoxyethane (DME), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and tetrahydrofuran (THF) were stored over 4A sieves. Acetonitrile (CH_3CN) was stored over 3A sieves. Organic layers from aqueous extractions were dried over $MgSO_4$ and concentrated in vacuo. Melting points are uncorrected. ^1H NMR spectra were determined at 300 MHz (Varian Unity 300 or XL 300 series NMR) and are reported in ppm downfield from internal tetramethylsilane (TMS) in $CDCl_3$ or DMSO-d_6. Significant ^1H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz, number of protons. IR spectra were recorded on a Perkin-Elmer 1600 Series FTIR as Nujol mulls. Chemical ionization mass spectra (CIMS) were recorded on a Finnegan-MAT TSQ4500 mass spectrometer using isobutane as carrier gas and recorded in units of m/z. High-resolution mass spectra (HRMS) were recorded on Cyanamid's FTICR[30] mass spectrometer using FAB techniques. Elemental analyses were performed by Microlit Laboratories, Caldwell, NJ. Flash chromatography was performed with 230–400-mesh silica gel 206 (ICN Biochemicals). Analytical thin-layer chromatography was done with glass-backed silica plates, 250 microns (Analtech).

Phenoxyaniline Synthesis. General Procedure. A heterogeneous mixture containing aminophenol **4** (100 mol %), benzotrifluoride **3** (100 mol %), and K_2CO_3 (150 mol %) were heated in the solvent and for the time indicated below (0.5–1 M). After TLC analysis (EtOAc/hexanes, 20/80) showed complete consumption of starting material, the reaction was cooled, diluted with ether, and washed with three to four portions of water, and the combined aqueous washes were back-extracted with ether. The combined organic phases were dried and concentrated. The resultant products were of sufficient purity to be used directly in the next step. Pure analytical samples were obtained by flash chromatography (EtOAc/hexanes).

***p*-[(2-Chloro-α,α,α-trifluoro-*p*-tolyl)oxy]aniline (5a).** *p*-Aminophenol and compound **3a**[31] were heated in DMF at 100 °C for 66 h to give 71% of a tan solid: mp 65–66.5 °C; ^1H NMR ($CDCl_3$) δ 7.69 (s, 1 H), 7.36 (d, J = 8.7, 1 H), 6.90–6.82 (m, 3 H), 6.70 (dd, J = 2.1, 6.6, 2 H), 3.65 (s, 2 H); IR 3498, 3396, 1631 cm^{-1}; CIMS 288 (MH^+). Anal. Calcd for $C_{13}H_9ClF_3NO$: C, 54.28; H, 3.15; N, 4.87. Found: C, 54.06; H, 3.22; N, 4.61.

***p*-[(2-Chloro-α,α,α,6-tetrafluoro-*p*-tolyl)oxy]aniline (5b).** *p*-Aminophenol and compound **3b**[31] were heated in CH_3CN at reflux for 25 h to give 84% of a tan solid: mp 55–57 °C; ^1H NMR ($CDCl_3$) δ 7.56 (d, J = 1.5, 1 H), 7.36 (d, J = 9.6, 1 H), 6.77 (dd, J = 1.9, 6.6, 2 H), 6.63 (dd, J = 1.9, 6.6, 2 H), 3.58 (s, 2 H); CIMS 306 (MH^+). Anal. Calcd for $C_{13}H_8ClF_4NO$: C, 51.08; H, 2.64; N, 4.58. Found: C, 51.09; H, 2.73; N, 4.48.

***m*-[(2-Chloro-α,α,α-trifluoro-*p*-tolyl)oxy]aniline (5c).** *m*-Aminophenol and compound **3a** were heated in DMF at 100 °C for 48 h to give 51% of a brown oil: ^1H NMR (DMSO-d_6) δ 7.92 (d, J = 1.8, 1 H), 7.66 (dd, J = 1.5, 8.4, 1 H), 7.13–7.04 (m, 2 H), 6.46 (dd, J = 2.1, 8.1, 1 H), 6.27 (t, J = 2.1, 1 H), 6.20 (dd, J = 2.4, 7.8, 1 H), 5.33 (s, 2 H); IR 3473, 3385, 1642, 1606 cm^{-1}. Anal. Calcd for $C_{13}H_9ClF_3NO$: C, 54.28; H, 3.15; N, 4.87. Found: C, 54.17; H, 3.31; N, 4.70.

***m*-[(2-Chloro-α,α,α,6-tetrafluoro-*p*-tolyl)oxy]aniline (5d).** *m*-Aminophenol and compound **3b** were heated in CH_3CN at reflux for 18 h to give 89% of a brown oil: ^1H NMR ($CDCl_3$) δ 7.60 (s, 1 H), 7.40 (d, J = 8.4, 1 H), 7.08 (t, J = 7.8, 1 H), 6.42 (d, J = 8.4, 1 H), 6.26–6.23 (m, 2 H), 3.73 (s, 2 H); HRMS calcd for $C_{13}H_9ClF_4NO$ (MH^+) 306.0309, found 306.0315.

Indolin-2-one Preparation from Anilines and Chlorosulfonium Salts. General Procedure. Ethyl (methylthio)acetate (110 mol %) was added to a −78 °C solution of chlorine (120 mol %) in CH_2Cl_2 (0.1–0.3 M) under an atmosphere of N_2. After 5–10 min, a CH_2Cl_2 solution of the appropriate aniline **5** (100 mol %) and triethylamine (100 mol %) was added (slight exotherm), and stirring was continued for 1–1.5 h. Triethylamine (150 mol %) was added, the solution was allowed to warm up to room temperature (1–2 h), and the salts that formed were removed by aqueous extraction. After drying and concentrating the organic phase, the crude amino ester (containing some unreacted aniline derivative) was dissolved in toluene and heated at reflux in the presence of *p*-toluenesulfonic acid (5 mol %) until cyclization was complete (usually 2–6 h). The desired product usually precipitated from the toluene upon cooling to room temperature. When a regioisomeric mixture was obtained (from the reaction of meta-substituted anilines), the crude product mixture was concentrated and the components were separated by flash chromatography.

5-[(2-Chloro-α,α,α-trifluoro-*p*-tolyl)oxy]-3-(methylthio)-indolin-2-one (7a). Aniline **5a** gave **7a** as a tan solid in 49% yield: mp 175–178 °C; ^1H NMR (DMSO-d_6) δ 10.30 (s, 1 H), 7.97 (s, 1 H), 7.67 (d, J = 9.0, 1 H), 7.08–6.90 (m, 4 H), 4.57 (s, 1 H), 1.98 (s, 3 H); IR 1733, 1706 cm^{-1}; CIMS 374 (MH^+). Anal. Calcd for $C_{16}H_{11}ClF_3NO_2S$: C, 51.41; H, 2.97; N, 3.75. Found: C, 51.16; H, 3.02; N, 3.68.

5-[(2-Chloro-α,α,α,6-tetrafluoro-*p*-tolyl)oxy]-3-(methylthio)indolin-2-one (7b). Aniline **5b** gave **7b** as a tan solid in 43% yield: mp 137–142 °C; ^1H NMR ($CDCl_3$) δ 9.59 (s, 1 H), 7.58 (s, 1 H), 7.41 (d, J = 9.0, 1 H), 7.01 (d, J = 2.1, 1 H), 6.90–6.79 (m, 2 H), 4.27 (s, 1 H), 1.98 (s, 3 H); IR 1724, 1710 cm^{-1}; CIMS 392 (MH^+). Anal. Calcd for $C_{16}H_{10}ClF_4NO_2S$: C, 49.05; H, 2.57; N, 3.58. Found: C, 48.82; H, 2.77; N, 3.57.

6-[(2-Chloro-α,α,α-trifluoro-*p*-tolyl)oxy]-3-(methylthio)-indolin-2-one (7c) and 4-[(2-Chloro-α,α,α-trifluoro-*p*-tolyl)-oxy]-3-(methylthio)indolin-2-one (7d). Aniline **5c** gave a mixture of **7c** (less polar) and **7d** (more polar) (EtOAc/hexanes, 1/2) which was separated by flash chromatography (EtOAc/hexanes, 10–25%).

7c: isolated as a tan solid in 40% yield; mp 131–133 °C; ^1H NMR (DMSO-d_6) δ 10.57 (s, 1 H), 8.03 (d, J = 1.5, 1 H), 7.71 (dd, J = 1.5, 7.8, 1 H), 7.30 (d, J = 8.4, 1 H), 7.22 (d, J = 8.4, 1 H), 6.68 (dd, J = 2.1, 7.8, 1 H), 6.50 (d, J = 2.1, 1 H), 4.53 (s, 1 H), 1.99 (s, 3 H); IR 1725, 1711, 1624, 1607 cm^{-1}. Anal. Calcd for $C_{16}H_{11}ClF_3NO_2S$: C, 51.41; H, 2.97; N, 3.75. Found: C, 51.25; H, 3.01, N. 3.65.

7d: isolated as a tan solid in 17% yield; mp 181–185 °C; ^1H NMR (DMSO-d_6) δ 10.74 (s, 1 H), 8.00 (d, J = 1.5, 1 H), 7.65 (dd, J = 1.5, 8.7, 1 H), 7.29 (t, J = 7.8, 1 H), 7.08 (d, J = 8.7, 1 H), 6.74 (d, J = 7.8, 1 H), 6.59 (d, J = 8.1, 1 H), 4.40 (s, 1 H), 1.92 (s, 3 H); IR 1712, 1680, 1625, 1596 cm^{-1}; CIMS 374 (MH^+). Anal. Calcd for $C_{16}H_{11}ClF_3NO_2S$: C, 51.41; H, 2.97; N, 3.75. Found: C, 51.41; H, 3.07; N, 3.56.

6-[(2-Chloro-α,α,α,6-tetrafluoro-*p*-tolyl)oxy]-3-(methylthio)indolin-2-one (7e) and 4-[(2-Chloro-α,α,α,6-tetrafluoro-*p*-tolyl)oxy]-3-(methylthio)indolin-2-one (7f). Aniline **5d** gave a mixture of **7e** (less polar) and **7f** (more polar) (EtOAc/hexanes, 1/2) which was separated by flash chromatograph (EtOAc/hexanes, 10–20%).

7e: isolated as a light pink solid in 36% yield; mp 144–145 °C; ^1H NMR ($CDCl_3$) δ 9.53 (s, 1 H), 7.55 (s, 1 H), 7.37 (d, J = 9.3, 1 H), 7.25 (d, J = 8.4, 1 H), 6.57 (dd, J = 2.7, 8.4, 1 H), 6.46 (d, J = 2.7, 1 H), 4.20 (s, 1 H), 1.94 (s, 3 H); IR 1713 (br), 1625, 1590 cm^{-1}; CIMS 392 (MH^+). Anal. Calcd for $C_{16}H_{10}ClF_4NO_2S$: C, 49.05; H, 2.57; N, 3.58. Found: C, 49.09; H, 2.58; N, 3.44.

7f: isolated as a tan solid in 14% yield; mp 201–202.5 °C; ^1H NMR ($CDCl_3$) δ 9.03 (br s, 1 H), 7.55 (s, 1 H), 7.36 (d, J = 9.3, 1 H), 7.11 (t, J = 8.1, 1 H), 6.67 (d, J = 8.1, 1 H), 6.17 (d, J = 7.8, 1 H), 4.46 (s, 1 H), 2.09 (s, 3 H); IR 1713, 1678, 1621, 1601 cm^{-1}; CIMS 392 (MH^+). Anal. Calcd for $C_{16}H_{10}ClF_4NO_2S$: C, 49.05; H, 2.57; N, 3.58. Found: C, 49.02; H, 2.49; N, 3.43.

C-3 Alkylation of 3-(Methylthio)indolin-2-ones. General Procedure. Sodium hydride (60% oil dispersion, 100 mol %) was added to a solution of 3-(methylthio)indolin-2-one **7** in DMSO (100 mol %, 0.1–0.3 M) under an atmosphere of N_2. After H_2 evolution was complete (usually 20–30 min), a solution of al-

(30) (a) Meek, J.; Stockton, G. U.S. Patent 4686365, 1987. (b) Millen, W.; Meek, J.; Wayne, R. 38th ASM Conference on Mass Spectrometry and Allied Topics, Tucson, AZ, June 1990.

(31) Compounds **3a** and **3b** were provided by PPG Industries, Inc.

kylating agent (100 mol %) in DMSO was added dropwise during 5 min. After TLC analysis (EtOAc/hexanes, 20/80) showed complete consumption of starting material (usually 1–4 h), the reaction mixture was diluted with Et_2O and washed with three to four portions of H_2O, and the aqueous phases were back-extracted with additional Et_2O. The organic phases were combined, dried, and concentrated, and the resultant crude products were purified by flash chromatography (EtOAc/hexanes).

5-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methyl-3-(methylthio)indolin-2-one (8a) was prepared from **7a** and methyl iodide as a beige solid in 60% yield: mp 167–171 °C; ^{1}H NMR ($CDCl_3$) δ 9.71 (s, 1 H), 7.73 (d, J = 1.5, 1 H), 7.41 (d, J = 7.5, 1 H), 7.09 (d, J = 2.1, 1 H), 7.03–6.88 (m, 3 H), 1.94 (s, 3 H), 1.68 (s, 3 H); IR 1724, 1681 cm^{-1}; CIMS 388 (MH^+). Anal. Calcd for $C_{17}H_{13}ClF_3NO_2S$: C, 52.65; H, 3.38; N, 3.61. Found: C, 52.62; H, 3.57; N, 3.61.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-methyl-3-(methylthio)indolin-2-one (8b) was prepared from **7b** and methyl iodide as a light brown solid in 69% yield: ^{1}H NMR ($CDCl_3$) δ 9.65 (s, 1 H), 7.58 (s, 1 H), 7.38 (d, J = 1.8, 1 H), 6.97 (d, J = 2.1, 1 H), 6.90 (d, J = 8.4, 1 H), 6.74 (dd, J = 2.7, 8.4, 1 H), 1.87 (s, 3 H), 1.64 (s, 3 H); IR 1712 cm^{-1}; CIMS 406 (MH^+). Anal. Calcd for $C_{17}H_{12}ClF_4NO_2S$: C, 50.32; H, 2.98; N, 3.45. Found: C, 50.42; H, 3.06; N, 3.32.

6-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methyl-3-(methylthio)indolin-2-one (8c) was prepared from **7c** and methyl iodide as a pink solid in 77% yield: mp 168–170 °C; ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1 H), 8.04 (d, J = 2.1, 1 H), 7.73 (d, J = 9.0, 1 H), 7.34 (d, J = 8.4, 1 H), 7.25 (d, J = 9.0, 1 H), 6.71 (dd, J = 2.4, 8.4, 1 H), 6.54 (d, J = 2.4, 1 H), 1.93 (s, 3 H), 1.55 (s, 3 H); IR 1732, 1687, 1630, 1605 cm^{-1}. Anal. Calcd for $C_{17}H_{13}ClF_3NO_2S$: C, 52.65; H, 3.38; N, 3.61. Found: C, 52.61; H, 3.33; N, 3.42.

4-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methyl-3-(methylthio)indolin-2-one (8d) was prepared from **7d** and methyl iodide as a tan solid in 50% yield: ^{1}H NMR ($CDCl_3$) δ 9.64 (br s, 1 H), 7.75 (s, 1 H), 7.47 (d, J = 8.4, 1 H), 7.22 (t, J = 8.4, 1 H), 7.05 (d, J = 8.4, 1 H), 6.83 (d, J = 7.5, 1 H), 6.47 (d, J = 8.4, 1 H), 1.96 (s, 3 H), 1.85 (s, 3 H); IR 1726, 1679, 1624, 1598 cm^{-1}; CIMS 388 (MH^+). Anal. Calcd for $C_{17}H_{13}ClF_3NO_2S$: C, 52.65; H, 3.38; N, 3.61. Found: C, 53.04; H, 3.30; N, 3.51.

5-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-isopropyl-3-(methylthio)indolin-2-one (8e) and 5-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-2-isopropoxy-3-(methylthio)indole (11). Treatment of **7a** with 2-bromopropane at room temperature overnight gave a mixture from which **8e** (more polar) and **11** (less polar) (EtOAc/hexanes, 40/60) were isolated.

8d: isolated as a tan powder in 26% yield; mp 182–185 °C; ^{1}H NMR ($CDCl_3$) δ 9.27 (br s, 1 H), 7.73 (d, J = 1.8, 1 H), 7.43 (dd, J = 1.8, 8.4, 1 H), 7.11 (d, J = 1.8, 1 H), 6.97–6.95 (m, 2 H), 6.85 (d, J = 8.4, 1 H), 2.42 (septet, J = 6.9, 1 H), 1.90 (s, 3 H), 1.19 (d, J = 6.9, 3 H), 0.88 (d, J = 6.9, 3 H); IR 1721, 1678 cm^{-1}; CIMS 416 (MH^+). Anal. Calcd for $C_{19}H_{17}ClF_3NO_2S$: C, 54.88; H, 4.12; N, 3.37. Found: C, 54.49; H, 4.10; N, 3.56.

11: isolated as a brown gum in 8% yield; ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1 H), 7.72 (s, 1 H), 7.36–7.33 (m, 2 H), 7.18 (d, J = 8.4, 1 H), 6.87–6.82 (m, 2 H), 5.26 (m, 1 H), 2.25 (s, 3 H), 1.41 (d, J = 4.5, 6 H); IR 2359, 2341, 1606, 1580, 1540 cm^{-1}; CIMS 416 (MH^+).

3-Benzyl-5-[(2-chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-(methylthio)indolin-2-one (8f) was prepared from **7a** and benzyl bromide as a tan solid in 78% yield: mp 174–177 °C; ^{1}H NMR ($CDCl_3$) δ 8.65 (br s, 1 H), 7.75 (d, J = 2.1, 1 H), 7.44 (d, J = 8.2, 1 H), 7.10–6.75 (m, 9 H), 3.47 (d, J = 15.0, 1 H), 3.21 (d, J = 15.0, 1 H), 1.99 (s, 3 H); IR 1731, 1681 cm^{-1}; CIMS 464 (MH^+); HRMS calcd for $C_{23}H_{18}ClF_3NO_2S$ (MH^+) 464.0699, found 464.0706.

Ethyl 5-[(2-chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-(methylthio)-2-oxo-3-indolineacetate (8g) was prepared from **7a** and ethyl bromoacetate as a tan solid in 81% yield: mp 138–143 °C; ^{1}H NMR ($CDCl_3$) δ 9.29 (s, 1 H), 7.71 (d, J = 2.1, 1 H), 7.40 (d, J = 8.4, 1 H), 7.03 (d, J = 1.8, 1 H), 6.97–6.93 (m, 2 H), 6.82 (d, J = 8.7, 1 H), 3.96 (q, J = 7.2, 2 H), 3.35 (d, J = 16.5, 1 H), 3.07 (d, J = 16.5, 1 H), 2.04 (s, 3 H), 1.08 (t, J = 7.2, 3 H); IR 1726 (br), 1603 cm^{-1}; CIMS 460 (MH^+). Anal. Calcd for $C_{20}H_{17}ClF_3NO_4S$: C, 52.24; H, 3.73; N, 3.05. Found: C, 51.94; H, 3.68; N, 2.97.

Ethyl 5-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-α-methyl-3-(methylthio)-2-oxo-3-indolineacetates (8h and 8i) and Ethyl 2-[[5-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-(methylthio)indol-2-yl]oxy]propionate (12). Treatment of **7a** with ethyl bromopropionate gave the following three products which were separated by flash chromatography (EtOAc/hexanes, 10–20%). The major product was the O-alkylated compound **12**. Two diastereomeric C-alkylated products were also obtained but the stereochemistry was not determined. The products are listed in order of increasing polarity (EtOAc/hexanes, 40/60).

12: isolated as a brown oil in 32% yield; ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1 H), 7.71 (s, 1 H), 7.33 (m, 2 H), 7.22 (d, J = 8.4, 1 H), 6.88–6.82 (m, 2 H), 5.49 (q, J = 6.9, 1 H), 4.29–4.20 (m, 2 H), 2.23 (s, 3 H), 1.69 (d, J = 6.9, 3 H), 1.30 (t, J = 7.2, 3 H); IR 1738 (br) cm^{-1}; CIMS 474 (MH^+).

8h: isolated as a beige solid in 14% yield; mp 130–135 °C; ^{1}H NMR ($CDCl_3$) δ 9.75 (br s, 1 H), 7.70 (s, 1 H), 7.40 (d, J = 8.4, 1 H), 7.35 (s, 1 H), 7.01–6.96 (m, 2 H), 6.87 (d, J = 8.4, 1 H), 4.11 (m, 2 H), 3.33 (q, J = 7.2, 1 H), 2.03 (s, 3 H), 1.19 (m, 6 H); CIMS 474 (MH^+); HRMS calcd for $C_{21}H_{20}ClF_3NO_4S$ (MH^+) 474.0754, found 474.0749.

8i: isolated as a yellow solid in 15% yield; mp 120–124 °C; ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1 H), 7.66 (s, 1 H), 7.37 (d, J = 8.4, 1 H), 7.10 (s, 1 H), 6.99–6.91 (m, 2 H), 6.80 (d, J = 8.4, 1 H), 3.93 (q, J = 6.9, 2 H), 3.33 (q, J = 7.5, 1 H), 2.02 (s, 3 H), 1.61 (d, J = 7.5, 3 H), 1.04 (t, J = 6.9, 3 H); IR 1732, 1704 cm^{-1}; CIMS 474 (MH^+).

N-Alkylation of 3-Alkyl-3-(methylthio)indolin-2-ones. General Procedure. The general procedure described for the C-alkylation of **7** was followed with a slight excess of sodium hydride and alkylating agent employed (110–120 mol %). The crude products were purified by flash chromatography (EtOAc/hexanes).

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-1,3-dimethyl-3-(methylthio)indolin-2-one (9a) was prepared from **8b** and methyl iodide as a yellow solid in 63% yield: mp 117–120 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1 H), 7.38 (dd, J = 1.8, 9.9, 1 H), 6.99 (d, J = 2.4, 1 H), 6.80 (dd, J = 2.4, 8.7, 1 H), 6.73 (d, J = 8.7, 1 H), 3.21 (s, 3 H), 1.89 (s, 3 H), 1.62 (s, 3 H); IR 1708 cm^{-1}; CIMS 420 (MH^+).

6-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-1,3-dimethyl-3-(methylthio)indolin-2-one (9b) was prepared from **8c** and methyl iodide as a white solid in 53% yield: ^{1}H NMR (DMSO-d_6) δ 8.03 (d, J = 2.4, 1 H), 7.71 (dd, J = 1.5, 8.7, 1 H), 7.39 (d, J = 8.1, 1 H), 7.18 (d, J = 8.4, 1 H), 6.98 (s, 1 H), 6.74 (d, J = 8.4, 1 H), 3.15 (s, 3 H), 1.92 (s, 3 H), 1.58 (s, 3 H); IR 1702 cm^{-1}. Anal. Calcd for $C_{18}H_{15}ClF_3NO_2S$: C, 53.80; H, 3.76; N, 3.49. Found: C, 53.68; H, 3.76; N, 3.49.

4-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-1,3-dimethyl-3-(methylthio)indolin-2-one (9c) was prepared from **8d** and methyl iodide as an amber solid in 64% yield: mp 109–110.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 1.2, 1 H), 7.46 (d, J = 8.7, 1 H), 7.27 (t, J = 8.1, 1 H), 7.03 (d, J = 8.7, 1 H), 6.69 (d, J = 7.8, 1 H), 6.49 (d, J = 8.7, 1 H), 3.26 (s, 3 H), 1.97 (s, 3 H), 1.82 (s, 3 H); IR 1727, 1708 cm^{-1}; CIMS 402 (MH^+). Anal. Calcd for $C_{18}H_{15}ClF_3NO_2S$: C, 53.80; H, 3.76; N, 3.49. Found: C, 53.85; H, 4.01; N, 3.37.

Ethyl 5-[(2-chloro-α,α,α-trifluoro-p-tolyl)oxy]-α,3-dimethyl-3-(methylthio)-2-oxo-1-indolineacetate (9d) was prepared from **8a** and ethyl bromopropionate as a brown oil in 70% yield and isolated as an inseparable mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1 H), 7.42 (dd, J = 1.2, 9.0, 1 H), 7.11 (m, 1 H), 6.95–6.88 (m, 2 H), 6.79, 6.76 (d, J = 9.0, 1 H), 5.22, 5.15 (q, J = 7.5, 1 H), 4.23–4.15 (m, 2 H), 1.92 (s, 3 H), 1.82 (s, 3 H), 1.64, 1.63 (d, J = 4.5, 3 H), 1.19, 1.17 (t, J = 7.2, 7.5, 3 H); IR 1731 (br) cm^{-1}; CIMS 488 (MH^+).

1-Benzyl-5-[(2-chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methyl-3-(methylthio)indolin-2-one (9e) was prepared from **8a** and benzyl bromide as an amber gum in 62% yield: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 1.8, 1 H), 7.41 (d, J = 8.4, 1 H), 7.33–7.29 (m, 6 H), 7.11 (d, J = 2.4, 1 H), 6.86 (d, J = 8.7, 1 H), 6.73 (d, J = 8.4, 1 H), 5.03 (d, J = 15.6, 1 H), 4.83 (d, J = 15.6, 1 H), 2.00 (s, 3 H), 1.71 (s, 3 H); IR 1722 (br) cm^{-1}; CIMS 478 (MH^+). Anal. Calcd for $C_{24}H_{19}ClF_3NO_2S$: C, 60.32; H, 4.01; N, 2.93. Found: C, 60.05; H, 4.21; N, 2.91.

5-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methyl-3-(methylthio)-2-oxo-1-indolineacetonitrile (9f) was prepared from **8a** and bromoacetonitrile as an amber oil in 61% yield: ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1 H), 7.45 (d, J = 8.7, 1 H), 7.15 (s, 1 H), 7.04 (br s, 2 H), 6.93 (d, J = 8.7, 1 H), 4.69 (d, J = 7.2, 2 H), 1.97 (s, 3 H), 1.69 (s, 3 H); CIMS 427 (MH^+). Anal. Calcd for $C_{19}H_{14}ClF_3N_2O_2S$: C, 53.46; H, 3.31; N, 6.56. Found: C, 53.75; H, 3.65; N, 6.15.

1-Allyl-5-[(2-chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methyl-3-(methylthio)indolin-2-one (9g) was prepared from **8a** and allyl bromide as a light brown oil in 65% yield: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 2.4, 1 H), 7.41 (dd, J = 2.1, 9.0, 1 H), 7.10 (d, J = 2.4, 1 H), 6.95 (dd, J = 2.4, 8.4, 1 H), 6.88 (d, J = 8.7, 1 H), 6.84 (d, J = 8.4, 1 H), 5.82 (m, 1 H), 5.26 (d, J = 5.4, 1 H), 5.22 (s, 1 H), 4.35 (m, 2 H), 1.95 (s, 3 H), 1.65 (s, 3 H); IR 1720, 1644, 1601 cm^{-1}; CIMS 427 (M^+); HRMS calcd for $C_{20}H_{18}ClF_3NO_2S$ (MH^+) 428.0699, found 428.0700.

5-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methyl-3-(methylthio)-1-(2-propynyl)indolin-2-one (9h) was prepared from **8a** and propargyl bromide as a tan solid in 66% yield: mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 2.4, 1 H), 7.42 (dd, J = 2.1, 8.7, 1 H), 7.11 (d, J = 2.1, 1 H), 7.07 (d, J = 8.4, 1 H), 7.00 (dd, J = 2.4, 8.4, 1 H), 6.91 (d, J = 8.4, 1 H), 4.60 (dd, J = 2.4, 19.2, 1 H), 4.44 (dd, J = 2.4, 19.2, 1 H), 2.27 (t, J = 2.4, 1 H), 1.91 (s, 3 H), 1.64 (s, 3 H); IR 2121, 1714, 1613 cm^{-1}; CIMS 426 (MH^+). Anal. Calcd for $C_{20}H_{15}ClF_3NO_2S$: C, 56.41; H, 3.55; N, 3.29. Found: C, 56.61; H, 3.55; N, 3.23.

Raney Nickel Desulfurization of 3-(Methylthio)indolin-2-ones. General Procedure. Raney nickel was added portionwise to a solution of the appropriate 3-(methylthio)indolin-2-one in ethanol (0.1–0.3 M) at room temperature. After TLC analysis (EtOAc/hexanes) showed complete consumption of starting material, the catalyst was filtered through a bed of Celite and washed with additional ethanol. The filtrate was concentrated, and the crude product was purified by flash chromatography (EtOAc/hexanes).

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]indolin-2-one (10a) was prepared from **7b** as a tan solid in 81% yield: ^{1}H NMR ($CDCl_3$) δ 9.31 (s, 1 H), 7.57 (s, 1 H), 7.38 (d, J = 9.0, 1 H), 6.78–6.68 (m, 3 H), 3.52 (s, 2 H); CIMS 346 (MH^+). Anal. Calcd for $C_{15}H_8ClF_4NO_2$: C, 52.12; H, 2.33; N, 4.05. Found: C, 51.92; H, 2.27; N, 3.92.

5-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methylindolin-2-one (10b) was prepared from **8a** as a tan solid in 48% yield: mp 155–158 °C; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1 H), 7.73 (d, J = 2.1, 1 H), 7.43 (d, J = 8.7, 1 H), 6.98 (s, 1 H), 6.93 (s, 2 H), 6.89 (d, J = 8.4, 1 H), 3.49 (q, J = 7.5, 1 H), 1.51 (d, J = 7.5, 3 H); IR 1701 cm^{-1}; CIMS 342 (MH^+). Anal. Calcd for $C_{16}H_{11}ClF_3NO_2$: C, 56.24; H, 3.25; N, 4.10. Found: C, 56.15; H, 3.46; N, 3.97.

3-Benzyl-5-[(2-chloro-α,α,α-trifluoro-p-tolyl)oxy]indolin-2-one (10c) was prepared from **8f** as a pale yellow solid in 58% yield: mp 133–136 °C; ^{1}H NMR ($CDCl_3$) δ 9.45 (s, 1 H), 7.71 (d, J = 2.1, 1 H), 7.42 (d, J = 8.7, 1 H), 7.19–7.12 (m, 6 H), 6.90 (s, 1 H), 6.78 (d, J = 8.7, 1 H), 6.39 (s, 1 H), 3.80 (dd, J = 5.1, 9.0, 1 H), 3.48 (dd, J = 5.1, 13.5, 1 H), 2.99 (dd, J = 9.0, 13.5, 1 H); IR 1714 cm^{-1}; CIMS 418 (MH^+). Anal. Calcd for $C_{22}H_{15}ClF_3NO_2$: C, 63.25; H, 3.62; N, 3.35. Found: C, 63.46; H, 3.72; N, 3.28.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-1,3-dimethylindolin-2-one (10d) was prepared from **9a** as a pale yellow solid in 84% yield: mp 91–94 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1 H), 7.37 (d, J = 8.7, 1 H), 6.89 (s, 1 H), 6.76 (dd, J = 2.4, 8.4, 1 H), 6.69 (d, J = 8.4, 1 H), 3.39 (q, J = 7.8, 1 H), 3.16 (s, 3 H), 1.43 (d, J = 8.7, 3 H); IR 1708 cm^{-1}; CIMS 374 (MH^+). Anal. Calcd for $C_{17}H_{12}ClF_4NO_2$: C, 54.63; H, 3.24; N, 3.75. Found: C, 54.96; H, 3.36; N, 3.62.

6-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-1,3-dimethylindolin-2-one (10e) was prepared from **9b** as a white solid in 84% yield: mp 110–111 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 1.5, 1 H), 7.44 (dd, J = 1.5, 8.7, 1 H), 7.19 (d, J = 7.8, 1 H), 6.99 (d, J = 8.7, 1 H), 6.64 (dd, J = 2.1, 7.8, 1 H), 6.57 (d, J = 2.1, 1 H), 3.42 (q, J = 7.2, 1 H), 3.16 (s, 3 H), 1.47 (d, J = 7.2, 3 H); CIMS 356 (MH^+). Anal. Calcd for $C_{17}H_{13}ClF_3NO_2$: C, 57.40; H, 3.68; N, 3.94. Found: C, 57.38; H, 3.61; N, 3.86.

4-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-1,3-dimethylindolin-2-one (10f) was prepared from **9c** as a white solid in 80% yield: mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 7.67 (s, 1 H), 7.37 (d, J = 8.1, 1 H), 7.19 (t, J = 8.1, 1 H), 6.89 (d, J = 9.0, 1 H), 6.62 (d, J = 7.8, 1 H), 6.47 (d, J = 8.1, 1 H), 3.38 (q, J = 7.2, 1 H), 3.15 (s, 3 H), 1.42 (d, J = 7.2, 3 H); CIMS 356 (MH^+). Anal. Calcd for $C_{17}H_{13}ClF_3NO_2$: C, 57.40; H, 3.68; N, 3.94. Found: C, 57.11; H, 3.48; N, 3.75.

1-Benzyl-5-[(2-chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methylindolin-2-one (10g) was prepared from **9e** as a tan solid in 81% yield: mp 112–115 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1 H), 7.39 (d, J = 8.1, 1 H), 7.31–7.25 (m, 5 H), 7.02 (s, 1 H), 6.89–6.85 (m, 2 H), 6.73 (d, J = 8.1, 1 H), 4.92 (s, 2 H), 3.55 (q, J = 7.2, 1 H), 1.54 (d, J = 7.2, 3 H); CIMS 432 (MH^+). Anal. Calcd for $C_{23}H_{17}ClF_3NO_2$: C, 63.97; H, 3.97; N, 3.24. Found: C, 63.81; H, 3.95; N, 3.14.

1-Allyl-5-[(2-chloro-α,α,α-trifluoro-p-tolyl)oxy]-3-methylindolin-2-one (10h). Deactivated Raney nickel (heated at reflux in acetone for 2 h) was added incrementally to a solution of **9g** to give **10h** as a tan solid in 73% yield: mp 94–97 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 1.8, 1 H), 7.39 (dd, J = 1.8, 9.0, 1 H), 6.99 (s, 1 H), 6.93 (dd, J = 2.1, 8.7, 1 H), 6.88 (d, J = 9.0, 1 H), 6.81 (d, J = 8.4, 1 H), 5.83 (m, 1 H), 5.25 (s, 1 H), 5.20 (d, J = 5.1, 1 H), 4.33 (br s, 2 H), 3.48 (q, J = 7.5, 1 H), 1.48 (d, J = 7.5, 3 H); IR 1716, 1650, 1599 cm^{-1}; CIMS 382 (MH^+). HRMS calcd for $C_{19}H_{16}ClF_3NO_2$ (MH^+) 382.0822, found 382.0822.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-methyl-1-(2-propynyl)indolin-2-one (10i). Zinc dust (0.42 g, 6.38 mmol) was added to a solution of **9h** (0.68 g, 1.60 mmol) in acetic acid (10 mL). After being heated to reflux for 1 h, the heterogeneous solution was cooled, diluted with water (50 mL) and brine (15 mL), and extracted twice with $CHCl_3$. Drying and concentrating the organic phase gave an off-white solid contaminated with a small amount of the N-allyl compound **10h** (approximately 15% by ^{1}H NMR integration). Recrystallization with Et_2O/hexanes gave 0.33 g (55%) of white needles: mp 144–145 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 1.5, 1 H), 7.42 (dd, J = 1.8, 8.7, 1 H), 7.07–6.98 (m, 3 H), 6.89 (d, J = 8.7, 1 H), 4.52 (dq, J = 2.4, 12.9, 2 H), 3.49 (q, J = 7.5, 1 H), 2.26 (t, J = 2.4, 1 H), 1.48 (d, J = 7.5, 3 H); IR 3299, 1718 cm^{-1}; CIMS 380 (MH^+). Anal. Calcd for $C_{19}H_{13}ClF_3NO_2$: C, 60.09; H, 3.45; N, 3.69. Found: C, 60.06; H, 3.58; N, 3.51.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-1,3-dimethyl-3-(ethoxymethyl)indolin-2-one (13) was prepared by the general procedure described for the preparation of **9** using bromomethyl ethyl ether as the alkylating agent to give 49% of a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1 H), 7.40 (d, J = 8.7, 1 H), 6.98 (s, 1 H), 6.77–6.72 (m, 2 H), 3.64 (d, J = 7.8, 1 H), 3.53 (d, J = 7.8, 1 H), 3.37 (q, J = 8.4, 2 H), 3.19 (s, 3 H), 1.35 (s, 3 H), 1.02 (t, J = 8.4, 3 H); IR 1725 cm^{-1}; CIMS 432 (MH^+). Anal. Calcd for $C_{20}H_{18}ClF_4NO_3$: C, 55.63; H, 4.20; N, 3.24. Found: C, 55.77; H, 4.28; N, 3.21.

5-[(2-Chloro-α,α,α-trifluoro-p-tolyl)oxy]-1-methylindolin-2-one (14). To a solution of **10a** (20.0 g, 58.1 mmol, 100 mol %) in toluene (150 mL) heated at 50–60 °C was added NaH (2.44 g, 61.1 mmol, 105 mol %) all at once. After H_2 evolution ceased (ca. 20 min) a solution of dimethyl sulfate (7.40 mL, 61.1 mmol, 105 mol %) in toluene (20 mL) was added during 5 min through a dropping funnel. After stirring at this temperature for 2–3 h, the reaction mixture was cooled and partitioned between EtOAc and H_2O. The phases were separated, the organic phase was washed with additional H_2O, and the combined aqueous phases were back-extracted with EtOAc. The organic phases were dried and concentrated to a solid which was purified by trituration in EtOAc/hexanes to give 77% of a tan solid: mp 111–112 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1 H), 7.39 (d, J = 9.3, 1 H), 6.88 (s, 1 H), 6.84 (d, J = 8.7, 1 H), 6.72 (d, J = 8.4, 1 H), 3.50 (s, 3 H), 3.19 (s, 2 H); IR 1708 cm^{-1}; CIMS 360 (MH^+). Anal. Calcd for $C_{16}H_{10}ClF_4NO_2$: C, 53.43; H, 2.80; N, 3.89. Found: C, 53.22; H, 2.82; N, 3.95.

Benzyl methanesulfonate (18) was prepared by the literature procedure[29] from benzyl alcohol (5.40 g) to give 7.90 g (85%) of a pale yellow liquid which was used without further treatment: ^{1}H NMR ($CDCl_3$) δ 7.42 (s, 5 H), 5.24 (s, 2 H), 2.91 (s, 3 H); CIMS 186 (MH^+).

Preparation of 3-Alkylideneindolin-2-ones. General Procedure. A solution containing the appropriate indolin-2-one and ketone (0.1–0.2 M) was heated at reflux with piperidine (200

mol %) for 16–24 h. After cooling, the reaction mixture was concentrated and the product was purified by flash chromatography (EtOAc/hexanes).

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-isopropylideneindolin-2-one (17). Heating **10a** in acetone containing piperidine (200 mol %) gave the desired product as a yellow solid in 74% yield: mp 194–195 °C; ^{1}H NMR ($CDCl_3$) δ 9.17 (s, 1 H), 7.57 (s, 1 H), 7.38 (dd, J = 1.5, 6.6, 1 H), 7.27 (d, J = 1.8, 1 H), 6.77 (d, J = 9.0, 1 H), 6.60 (dd, J = 1.8, 8.4, 1 H), 2.61 (s, 3 H), 2.33 (s, 3 H); IR 1709, 1621, 1592 cm^{-1}; CIMS 386 (MH^+). Anal. Calcd for $C_{18}H_{12}ClF_4NO_2$: C, 56.05; H, 3.14; N, 3.63. Found: C, 56.01; H, 3.20; N, 3.51.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-isopropylidene-1-methylindolin-2-one (15a) was prepared as a beige solid in 78% yield by heating **14** and piperidine (200 mol %) in acetone at reflux: mp 121–124 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1 H), 7.38 (dd, J = 2.1, 9.6, 1 H), 7.31 (s, 1 H), 6.63 (s, 2 H), 3.21 (s, 3 H), 2.63 (s, 3 H), 2.34 (s, 3 H); IR 1686, 1621 cm^{-1}; CIMS 400 (MH^+). Anal. Calcd for $C_{19}H_{14}ClF_4NO_2$: C, 57.09; H, 3.53; N, 3.51. Found: C, 57.02; H, 3.68; N, 3.52.

Alternatively, **15a** was prepared by treatment of **17** with dimethyl sulfate to give **15a** in 69% yield. See N-Alkylation of 3-Alkylidene-Substituted Indolin-2-ones below.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-cyclopentylidene-1-methylindolin-2-one (15b) was prepared as a yellow solid in 82% yield by treatment of **14** with cyclopentanone (500 mol %) and piperidine (200 mol %) in toluene at reflux: mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1 H), 7.39 (d, J = 9.3, 1 H), 7.18 (s, 1 H), 6.67 (br s, 2 H), 3.23 (s, 3 H), 3.15 (br s, 2 H), 2.81 (br s, 2 H), 1.86 (br s, 4 H); IR 1694, 1640, 1624 cm^{-1}; CIMS 426 (MH^+). Anal. Calcd for $C_{21}H_{16}ClF_4NO_2$: C, 59.24; H, 3.79; N, 3.29. Found: C, 58.96; H, 3.93; N, 3.30.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-cyclohexylidene-1-methylindolin-2-one (15c) was prepared as a yellow solid in 73% yield by treatment of **14** with cyclohexanone (500 mol %) and piperidine (200 mol %) in toluene at reflux: mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1 H), 7.42 (s, 1 H), 7.36 (d, J = 9.0, 1 H), 6.62–6.58 (m, 2 H), 3.35 (t, J = 5.7, 2 H), 3.16 (s, 3 H), 2.78 (t, J = 5.7, 2 H), 1.80–1.66 (m, 6 H); IR 1684, 1611 cm^{-1}; CIMS 440 (MH^+). Anal. Calcd for $C_{22}H_{18}ClF_4NO_2$: C, 60.08; H, 4.13; N, 3.18. Found: C, 60.31; H, 4.23; N, 3.09.

N-Alkylation of 3-Alkylidene-Substituted Indolin-2-ones. A solution of **17**, K_2CO_3 (125 mol %), and the appropriate alkylating agent (110 mol %) was heated at reflux in 2-butanone (ca. 0.1 M) for 24 h. After cooling, the reaction mixture was partitioned between EtOAc and H_2O. The phases were separated, the aqueous phase was back-extracted, and the combined organic phases were dried and concentrated. The residue which contained the desired product and some unreacted starting material was purified by flash chromatography (EtOAc/hexanes, 15/85).

Ethyl 5-[(2-chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-isopropylidene-α-methyl-2-oxo-1-indolineacetate (15d) was prepared from **17** and ethyl bromoacetate as a yellow solid in 46% yield: mp 142–144 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1 H), 7.38 (dd, J = 1.8, 8.4, 1 H), 7.33 (d, J = 1.8, 1 H), 6.63 (dd, J = 2.4, 8.7, 1 H), 6.56 (d, J = 8.4, 1 H), 4.47 (s, 2 H), 4.20 (q, J = 7.2, 2 H), 2.63 (s, 3 H), 2.36 (s, 3 H), 1.25 (t, J = 7.2, 3 H); IR 1744, 1736, 1694, 1636, 1616 cm^{-1}; CIMS 472 (MH^+). Anal. Calcd for $C_{22}H_{18}ClF_4NO_4$: C, 56.00; H, 3.85; N, 2.97. Found: C, 55.95; H, 3.86; N, 3.03.

Reduction of 3-Alkylidene-Substituted Indolin-2-ones. General Procedure. A solution of the appropriate alkylidene-substituted indolin-2-one in DME/EtOH (1/1) was hydrogenated over PtO_2 (5–10 wt %) at 50 psi until reduction was complete (usually 4–7 h). The catalyst was filtered, washed with fresh EtOH, and concentrated to afford essentially pure material.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-isopropyl-1-methylindolin-2-one (16a) was obtained from the reduction of **15a** as a tan solid in 90% yield: mp 76–79 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1 H), 7.37 (d, J = 9.3, 1 H), 6.96 (s, 1 H), 6.77–6.69 (m, 2 H), 3.33 (d, J = 3.3, 1 H), 3.16 (s, 3 H), 2.49–2.41 (m, 1 H), 1.02 (d, J = 6.9, 3 H), 0.86 (d, J = 6.9, 3 H); IR 1697, 1624, 1603 cm^{-1}; CIMS 402 (MH^+); HRMS calcd for $C_{19}H_{17}ClF_4NO_2$ (MH^+) 402.0884, found 402.0883.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-cyclopentyl-1-methylindolin-2-one (16b) was obtained from the reduction of **15b** as a white solid in 91% yield: mp 114–117 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1 H), 7.37 (d, J = 9.3, 1 H), 6.99 (s, 1 H), 6.77–6.69 (m, 2 H), 3.48 (d, J = 4.8, 1 H), 3.16 (s, 3 H), 2.46–2.40 (m, 1 H), 1.86–1.33 (m, 8 H); IR 1697, 1625, 1599 cm^{-1}; CIMS 428 (MH^+). Anal. Calcd for $C_{21}H_{18}ClF_4NO_2$: C, 58.96; H, 4.24; N, 3.27. Found: C, 58.64; H, 4.35; N, 3.18.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-cyclohexyl-1-methylindolin-2-one (16c) was obtained from the reduction of **15c** as a beige solid in 90% yield; mp 95–102 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (s, 1 H), 7.35 (d, J = 9.6, 1 H), 6.97 (s, 1 H), 6.71–6.62 (m, 2 H), 3.28 (br s, 1 H), 3.12 (s, 3 H), 2.11–2.04 (m, 1 H), 1.70–1.12 (m, 10 H); IR 1704, 1625, 1605 cm^{-1}; CIMS 442 (MH^+). Anal. Calcd for $C_{22}H_{20}ClF_4NO_2$: C, 59.80; H, 4.56; N, 3.17. Found: C, 59.39; H, 4.55; N, 3.13.

Ethyl 5-[(2-chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-isopropyl-α-methyl-2-oxo-1-indolineacetate (16d) was obtained from the reduction of **15d** as a yellow solid in 98% yield: mp 85–88 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (s, 1 H), 7.31 (dd, J = 2.1, 9.9, 1 H), 6.92 (d, J = 1.8, 1 H), 6.69 (dd, J = 2.4, 8.4, 1 H), 6.52 (d, J = 8.7, 1 H), 4.52 (d, J = 17.1, 1 H), 4.19 (d, J = 17.1, 1 H), 4.12 (q, J = 7.2, 2 H), 3.37 (d, J = 3.3, 1 H), 2.48–2.38 (m, 1 H), 1.66 (t, J = 7.2, 3 H), 0.99 (d, J = 6.6, 3 H), 0.88 (d, J = 6.6, 3 H); IR 1742, 1709 cm^{-1}; CIMS 474 (MH^+). Anal. Calcd for $C_{22}H_{20}ClF_4NO_4$: C, 55.76; H, 4.25; N, 2.96. Found: C, 56.03; H, 4.54; N, 2.71.

5-[(2-Chloro-α,α,α,6-tetrafluoro-p-tolyl)oxy]-3-isopropylindolin-2-one (16e) was obtained from the reduction of **17** as a pale yellow solid in 84% yield: mp 139–141 °C; ^{1}H NMR ($CDCl_3$) δ 9.56 (s, 1 H), 7.57 (s, 1 H), 7.38 (d, J = 9.3, 1 H), 6.95 (s, 1 H), 6.83 (d, J = 8.4, 1 H), 6.71 (d, J = 8.4, 1 H), 3.40 (d, J = 3.0, 1 H), 2.50–2.44 (m, 1 H), 1.08 (d, J = 6.6, 3 H), 0.93 (d, J = 6.6, 3 H); IR 1705, 1688 cm^{-1}; CIMS 388 (MH^+). Anal. Calcd for $C_{18}H_{14}ClF_4NO_2$: C, 55.76; H, 3.64; N, 3.61. Found: C, 56.02; H, 3.78; N, 3.44.

A New Bis(indole) Alkaloid from a Deep-Water Marine Sponge of the Genus *Spongosorites*

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A number of bis(indole) alkaloids have been reported from the marine environment over the past few years. Some examples reported from sponges include: the topsentins reported from *Topsentia genitrix*,[1] *Spongosorites* spp.,[2] and *Hexadella* sp.,[3] which have a ketone and imidazole spacer between the two indole rings; the dragmacidins reported from both *Dragmacidon* sp.[4] and *Hexadella* sp.[5] which have a piperazine spacer; the nortopsentins reported from a *Spongosorites* sp. which lack the ketone observed in the topsentins;[6] and fascaplysin, a fully aromatized compound reported from *Fascaplysinopsis* sp.[7] Bis(indole) alkaloids have also been reported from the ascidians *Dendroda grossularia*[8] and *Didemnum candi-*

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