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Development of a Novel, Highly Efficient Halide-Catalyzed Sulfenylation of Indoles

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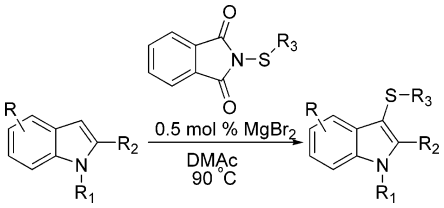
ABSTRACT

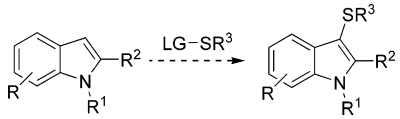


The reaction of a variety of indoles with *N*-thioalkyl- and *N*-thioarylphthalimides to produce 3-thioindoles is reported. Catalytic quantities of halide-containing salts are crucial to the success of this reaction. This highly efficient reaction provides sulfenylated indoles from bench-stable, readily available starting materials in good to excellent yields.

Sulfenylated indole motifs are ubiquitous in many biologically important compounds.[1a−d] In particular, the therapeutic value of numerous 3-thioindoles has been assessed in several disease areas, including obesity,[1a] cancer,[1b] heart disease,[1c] and bacterial infection.[1d] Preparation of such compounds is generally achieved by electrophilic aromatic sulfenylation chemistry. Sulfenylating agents such as disulfides,[2a] sulfenyl halides,[3b] and quinone mono-*O*,*S*-acetals[4c] have all been employed in this reaction, but are often impractical on both small and large scale due to the accessibility, substrate compatibility, and stability of these reagents. To overcome these problems, sulfenylations utilizing thiols activated in situ by *N*-chlorosuccinimide[5] or transition-metal catalysts[6] have been developed.

In the context of an ongoing drug discovery program, we required an efficient sulfenylation method that could be carried out on a range of electronically distinct indoles, using bench-stable sulfenylating agents at relatively high concentration (Scheme 1).[7]

Scheme 1



To date, however, no general sulfenylation protocol has been reported that is economical with respect to the sulfur component,[8] avoids the use of harsh chlorination conditions,[6]

(1) (a) Acton, J. L.; Meinke, P. T.; Wood, H.; Black, R. M. PCT Int. Appl. WO 2004/019869 A2, 2004. (b) (i) Avis, I.; Martínez, A.; Tauler, J.; Zudaire, E.; Mayburd, A.; Abu-Ghazaleh, R.; Ondrey, F.; Mulshine, J. L. *Cancer Res.* **2005**, *65*, 4181. (ii) De Martino, G.; La Regina, G.; Coluccia, A.; Edler, M. C.; Barbera, M. C.; Brancale, A.; Wilcox, E.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2004**, *47*, 6120. (c) Funk, C. D. *Nat. Rev. Drug Discovery* **2005**, *4*, 664. (d) Khandekar, S. S.; Gentry, D. R.; Van Aller, G. S.; Doyle, M. L.; Chambers, P. A.; Konstantinidis, A. K.; Brandt, M.; Daines, R. A.; Lonsdale, J. T. *J. Biol. Chem.* **2001**, *276*, 30024.

(2) (a) Atkinson, J. G.; Hamel, P.; Girard, Y. *Synthesis* **1988**, 480. (b) (i) Scoffone, E.; Fontana, A.; Rocchi, R. *Biochemistry* **1968**, *7*, 971. (ii) Anzai, K. *J. Heterocycl. Chem.* **1979**, *16*, 567. (c) Matsugi, M.; Murata, K.; Gotanda, K.; Nambu, H.; Anilkumar, G.; Matsumoto, K.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 2434.

(3) Schlosser, K. M.; Krasutsky, A. P.; Hamilton, H. W.; Reed, J. E.; Sexton, K. *Org. Lett.* **2004**, *6*, 819.

(4) Maeda, Y.; Koyabu, M.; Nishimura, T.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 7688.

(5) For sulfenylations utilising and/or liberating >1 equiv of sulfide, see refs 3 and 4.

(6) In our hands, sulfenylations involving the use of SO_2Cl_2 (ref 2b, ii) or NCS (ref 3) gave significant quantities of 3-chloroindole byproducts.

(7) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363.

(8) Kuehen, M. E. *J. Org. Chem.* **1963**, *28*, 2124.

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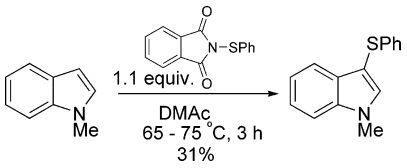
and is compatible with sensitive functionality. Having investigated several of the existing procedures,[2−4] we surveyed the literature for appropriate sulfenylating agents to meet our needs. Of particular interest were several reports detailing the sulfenylation of enolates[7] and enamines[8] using readily prepared,[9] stable thiophthalimide reagents. Furthermore, the reaction of a thiosuccinimide reagent with an indole moiety had been observed; however, stoichiometric quantities of $BF_3{\cdot}OEt_2$ in refluxing methylene chloride were required to achieve any appreciable conversion.[10] Prompted by these reports, we sought to develop a more benign and general sulfenylation protocol that circumvented the need for large quantities of strong Lewis acids or chlorinating reagents. Herein, we report the successful outcome of our investigations into this reaction.

Our initial investigations focused on establishing reactivity between *N*-methylindole and phenylthiophthalimide. We quickly determined that the reaction was sluggish at temperatures below 70 °C, perhaps due to the insolubility of the thiophthalimide reagent. Initial solvent screens[11] showed that polar solvents were essential for reactivity, with dimethylacetamide (DMAc) proving optimal (Scheme 2).

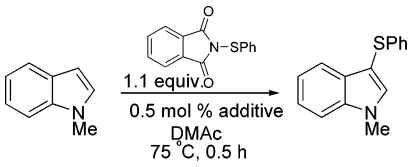
Scheme 2. Initial Result



Although after 24 h the reaction in DMAc would reach completion, with more sensitive substrates significant quantities of reagent decomposition or byproduct formation were observed.[12]

In an attempt to accelerate the reaction, we probed the effect of Lewis and Brønsted acid additives on the reaction (Table 1).

Table 1. Survey of Catalytic Brønsted and Lewis Acid Sources



additive	assay yield (%)	additive	assay yield (%)
none	13	$TiCl_4$	29
$TsOH{\cdot}OH_2$	10	$AlCl_3$	36
AcOH	12	$MgCl_2$	38
$BF_3{\cdot}OEt_2$	8	$MgBr_2$	54
NaCl	13	LiBr	48
KCl	11	LiCl	49

Unfortunately, protic acids had no pronounced effect on the reaction, and potassium chloride and sodium chloride were also ineffective catalysts, possibly due to their insolubility in DMAc. Interestingly, however, trace amounts of hard Lewis acids such as $MgBr_2$ and LiCl effectively promoted the transformation. Indeed, as detailed in Figure 1, when

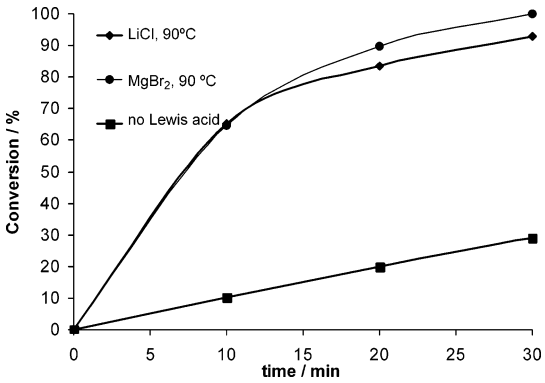
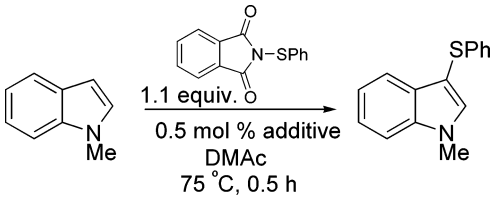


Figure 1. Effect of hard Lewis acids on the rate of reaction.

compared with the control experiment at 90 °C reaction times were cut from 24 h to 30 min, clearly indicating that catalysis is occurring.

Table 2. Effect of Catalytic Non-metal Halide Salts on the Reaction



additive	assay yield (%)	additive	assay yield (%)
$LiBF_4$	12	Bu_4NCl	43
$Bu_4NCl + LiBF_4$	43	Bu_4NBr	40

At this point, we postulated that a simple Lewis acid catalyzed mechanism was in operation, where the hard metal center was coordinating to the phthalimide carbonyl, thus weakening the N−S bond and increasing the electrophilicity of the sulfur.

Based on this hypothesis, we believed that metal salts bearing noncoordinating counterions would prove to be more effective catalysts. Surprisingly, however, lithium tetrafluoroborate failed to promote the reaction. However, when

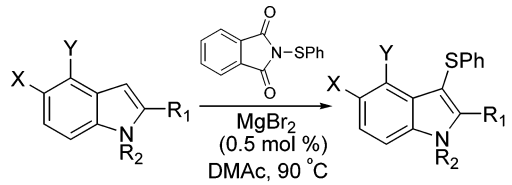
(9) For a convenient synthesis of thiophthalimide reagents, see: Klose, J.; Reese, C. B.; Song, Q. *Tetrahedron* **1997**, *53*, 14411.

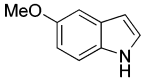
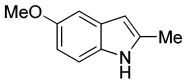
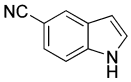
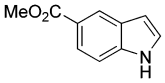
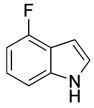
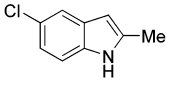
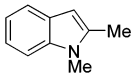
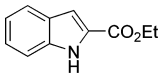
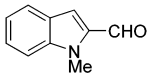
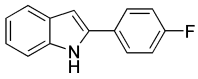
(10) Silvestri, R.; De Martino, G.; La Regina, G.; Artico, M.; Massa, S.; Vargiu, L.; Mura, M.; Loi, A. G.; Marceddu, T.; La Colla, P. *J. Med. Chem.* **2003**, *46*, 2482.

(11) For details regarding solvents screened, see the Supporting Information.

(12) Over extended reaction times diphenyl disulfide was observed.

Table 3. Indole Scope and Limitations



entry	indole	time (h)	assay yield(%)	isolated yield(%)
1		2.5	92	92
2		2	-	94
3		5	87	85
4		18	91	89
5		20	-	93
6		6	95	88
7		2.5	-	93
8		0.75	99	97
9		24	98	85[a]
10		72	78	45[a]
11		3	-	97

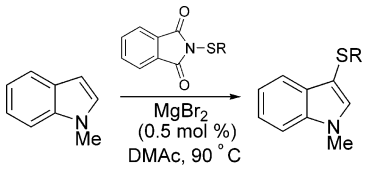
[a] Reaction was performed at 120 °C.

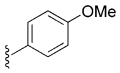
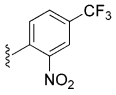
tetrabutylammonium chloride was added during the course of the reaction, a significant increase in conversion was observed (Table 2).

We therefore assumed the reaction was being promoted by the halide counterion rather than the metal. Consequently, we attempted the reaction in the presence of catalytic tetrabutylammonium halide salts. In all cases, reactivity almost comparable to the metal salts was observed, indicating that the halide counterion was indeed the catalytically active species.

With our optimized set of conditions in hand, we began to assess the scope and limitations of the reaction. As can be seen in Table 3, a wide variety of indoles can be sulfenylated, including the less reactive indole-2-carboxylates and 2-formyl-indoles (entries 9 and 10, respectively). Furthermore, indoles containing potentially base and/or Lewis acid sensitive functionalities such as nitriles, carboxylic esters, aromatic chlorides, and aldehydes were effectively sulfenylated in good yields (entries 4, 5, 7, and 10).

Table 4. Thiophthalimide Scope



entry	R	time (h)	isolated yield (%)
1	Me	1	93
2	2-cyanoethyl	1.5	98
3	^{i}Pr	19	94
4	*c*Hex	16	96
5	Ph	0.75	98
6	2-Pyr	2	96
7		1	97
8		20	98[a]

[a] Reaction performed at 100 °C.

Having established the scope with respect to the indole moiety, we next turned our attention to the thiophthalimide component (Table 4). Gratifyingly, a range of alkyl and aryl thiophthalimide reagents were effective sulfenylating agents. Again, potentially base or Lewis acid sensitive functionalities (entry 2) were well tolerated under the reaction conditions. Thiophthalimide reagents containing hindered alkyl groups such as isopropyl and cyclohexyl reacted smoothly to provide the corresponding sulfenylated indole product (entries 3 and 4).

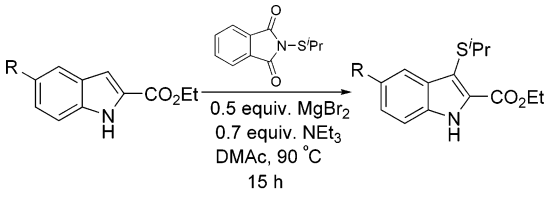
After demonstrating the reaction with a range of thiophthalimide moieties, we began to assess more challenging substrate combinations.

For example, the sulfenylation of indole-2-carboxylates with a sulfur-transfer reagent bearing a hindered alkyl group has proved to be a particularly difficult transformation.[3,4]

Under our standard reaction conditions, 2-carboxyethylindole reacted sluggishly (~5% conversion over 24 h), resulting in the increased decomposition of the reagent and formation of unwanted byproducts. To increase the reactivity of the indole, we screened a range of common bases.

We were pleased to find that NEt_3 in combination with $MgBr_2$ successfully promoted the reaction (Scheme 3). Under our modified conditions, indole-2-carboxylates react smoothly with *N*-(isopropyl)thiophthalimide in the presence of 0.5 equivalents of $MgBr_2$ and 0.7 equivalents of NEt_3 to afford previously inaccessible sulfenylated indoles in good yield.

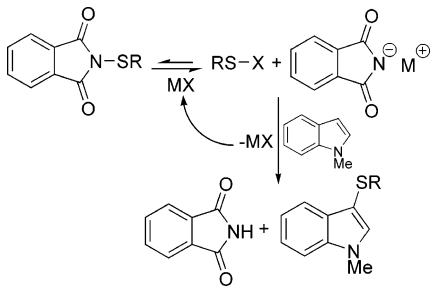
Scheme 3. Sulfenylation of Deactivated Indoles with Hindered Thiophthalimide Reagents



R	assay yield (%)	isolated yield (%)
H	100	98
Cl	100	89
OMe	99	86

Studies are now underway to extend this methodology to other aromatic systems and determine the role of the halide in the reaction. The proposed mechanism, shown in Scheme 4, details our current hypothesis where catalytic quantities of halide salt can react with the *N*-thiophthalimide reagent to produce the transient sulfenyl halide. This then undergoes reaction with the indole moiety to produce the sulfenylated product.

Scheme 4. Proposed Mechanism for Halide-Catalyzed Sulfenylation



In summary, we have developed an efficient, general indole sulfenylation protocol that is catalytic in halide. Most notably, this procedure can be used to sulfenylate deactivated indoles with sterically demanding sulfur groups in an efficient manner.

Acknowledgment. We thank Tom Novak (Merck & Co. Rahway, N.J.) for obtaining mass spectral data.

Supporting Information Available: Experimental information and data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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