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A Highly Efficient Procedure for 3-Sulfenylation of Indole-2-carboxylates

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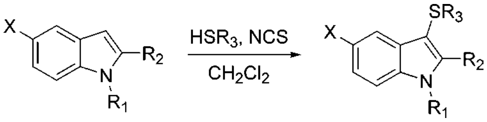
ABSTRACT



A highly efficient one-pot procedure for 3-sulfenylation of 2-carboxyindoles is described. Treatment of thiols with *N*-chlorosuccinimide at −78 °C in CH_2Cl_2 affords sulfenyl chlorides in situ that readily react with 2-carboxyindoles to give 3-thioindoles in high yields. This new method is milder, produces less waste, and is compatible with a wide range of thiol and indole functionality.

Substituted indole-2-carboxylates, more specifically 3-thioindole-2-carboxylates, have been explored for their therapeutic worth in many fields including the treatment of HIV[1] and obesity[2] as well as their use as endothelin antagonists[3] and anti-allergy agents.[4] The functionalization of the 3-position of indole-2-carboxylates relies on the nucleophilicity of that position.[5] Successful sulfur substitution at the 3-position has been described using various forms of electrophilic sulfur including disulfides[6] and sulfenyl chlorides.[7] There are disadvantages to each of these techniques. While the oxidation of thiols to the disulfides using sodium perborate works cleanly in near-quantitative yields,[8] the subsequent reaction with the indole produces an equivalent of thiol as an undesired byproduct. Formation of the sulfenyl chloride using sulfuryl chloride or chlorine often results in poor yields and is limited by the stability of the resulting sulfenyl chloride. These harsh chlorinations are also incompatible with certain functionalities. The formation of sulfenyl chlorides using *N*-chlorosuccinimide has been reported.[9] This milder method of chlorination expanded the scope of functional group compatibility enabling the formation of thermally unstable aliphatic sulfenyl chlorides, including those with ester groups.[10] By applying this methodology, we sought to find an efficient technique for the introduction of sulfur into a series of indole-2-carboxylates.

We found that the preparation of sulfenyl chlorides using *N*-chlorosuccinimide can be successfully applied to the direct functionalization of indoles. We herein describe a general and improved one-step method of sulfenylation of 2-car-

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[1] (a) Williams, T. M.; Ciccarone, T. M.; Saari, W. S.; Wai, J. S.; Greenlee, W. J.; Balani, S. K.; Goldman, M. E.; Hoffman, J. M., Jr.; Lumma, W. C., Jr.; Huff, J. R.; Rooney, C. S.; Sanderson, P. E.; Theoharides, A. D. PCT Int. Appl. WO 9419321, 1994. (b) Silvestri, R.; Artico, M.; Bruno, B.; Massa, S.; Novellino, E.; Greco, G.; Marongiu, M. E.; Pani, A.; De Montis, A.; La Colla, P. *Antivir. Chem. Chemoth.* **1998**, *9*, 139−148.

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[3] Berryman, K. A.; Bunker, A. M.; Doherty, A. M.; Edmunds, J. J. U.S. Patent 5482960, 1996.

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[5] Indoles: *Heterocyclic compounds*; Wiley: New York, 1972; Parts 1−3.

[6] (a) Bunker, A. M.; Edmunds, J. J.; Berryman, K. A.; Walker, D. M.; Flynn, M. A.; Welch, K. M.; Dohery, A. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1367−1370. (b) Anzai, K. *J. Heterocycl. Chem.* **1979**, *16*, 567−569. (c) Plate, R.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron* **1986**, *42*, 4503−4509.

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[8] Atkinson, J. G.; Hamel, P.; Girard, Y. *Synthesis* **1988**, 480−481.

[9] (a) Kroll, F.; Morphy, R.; Rees, D.; Gani, D. *Tetrahedron Lett.* **1997**, *38*, 8573−8576. (b) Aszodi, J.; Chantot, J. F.; Collard, J.; Teutsch, G. *Heterocycles* **1989**, *28*, 1061−1076.

[10] Seliger, H.; Goertz, H. H. *Synth. Commun.* **1980**, *10*, 175−182.

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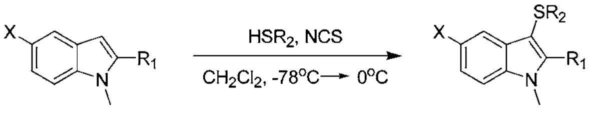
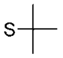
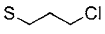
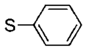
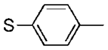
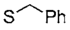
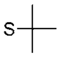
boxyindoles using in situ generated sulfenyl chlorides from a variety of thiols using *N*-chlorosuccinimide in methylene chloride (Table 1).[11]

Table 1. Sulfenylations of 1-Methylindole-2-carboxylates



1 2

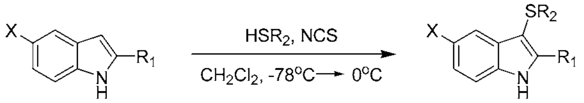
entry	X	R1	HS-R2	yield
1	OMe	CO_2Me		0
2	OMe	CO_2Me		86
3	OMe	CO_2Me		99
4	OMe	$CONH_2$		96
5	OMe	$CONH_2$		91
6	OMe	$CONH_2$		0

The advantages of this procedure include milder conditions than corrosive chlorine or sulfuryl chloride, as well as fast reaction times, easy workup, and improved yields. The in situ formation of the sulfenyl chlorides using *N*-chlorosuccinimide also enhances the scope of the reaction. The methodology was previously restricted by the stability and ease of isolation of the desired sulfenyl chlorides. This technique also avoids the formation of 1 equiv of thiol waste that occurs when using a disulfide as the electrophilic sulfur source.

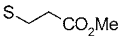
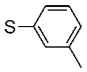
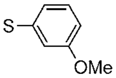
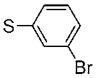
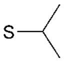
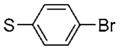
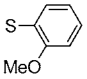
The scope of this method is further expanded because the indole nitrogen need not be protected. There is no significant difference in yields when comparing protected and unprotected indole cores (Table 2).

As shown by the results, the one noted limitation of the proposed sulfenylation, similar to any nucleophilic substitution, is a steric restriction. Entries 1, 6, and 12 of Tables 1 and 2 illustrate that this method gives no reaction for the isopropyl and *tert*-butyl thiols.

Table 2. Sulfenylations of Indole-2-carboxylates[12]

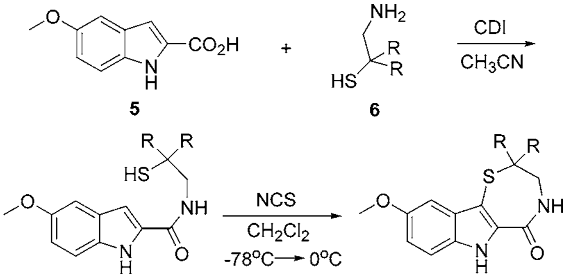


3 4

entry	X	R1	HS-R2	yield
7	OMe	CO_2Me		94
8	OMe	CO_2Me		97
9	H	CO_2Et		81*
10	H	CO_2Et		76*
11	H	CO_2Et		64*
12	H	CO_2Et		0
13	F	CO_2Me		51*
14	F	CO_2Me		48*

It was shown that these reaction conditions could also be used for intramolecular sulfenylation (Scheme 1). Thioamide **7** was prepared from the corresponding indole- 2-carboxylic acid **5** and 2-aminothioethane **6** via CDI amidation conditions.[13] Reaction with NCS leads to cyclization and formation of previously unavailable thioazepines **8**. The intramolecular

Scheme 1. Intramolecular Sulfenylations



7a: R=H; 89%
7b: R=Me, 95%

8a: R=H; 75%
8b: R=Me, 60%

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[11] Hamilton, H. W.; Krasutsky, A.; Reed, J. E.; Schlosser, K. M.; Sexton, K. E. Pat. Appl. 60/400092, 2002.

[12] Typical procedure (Table 2, entry 10): To a cooled solution of *N*-chlorosuccinimide (4.23 g, 31.7 mmol) in dichloromethane (250 mL) at −78 °C was added 3-methoxythiophenol (3.93 mL, 31.7 mmol). The reaction was warmed to 0 °C over 15 min, and a solution of indole-2-carboxylic acid ethyl ester (5 g, 26.4 mmol) in dichloromethane (50 mL) was added. The reaction was stirred at 0 °C for 1 h and then concentrated under reduced pressure. The residue was suspended in H_2O (150 mL) and stirred for 1 h. The solid was filtered and recrystallized from ethyl acetate/hexanes to yield the desired product (6.56 g, 76%): 400 MHz ^1H NMR (DMSO-d_6) δ 7.51 (d, 1H, $J = 8.3$ Hz), 7.41 (d, 1H, $J = 8.3$ Hz), 7.29 (m, 1H), 7.08 (m, 2H), 6.64 (d, 1H, $J = 7.8$ Hz), 6.55 (m, 2H), 4.28 (q, 2H, $J = 7.1$ Hz), 3.60 (s, 3H), 1.21 (t, 3H, $J = 7.1$ Hz); MS m/z 328 (M + 1). Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28. Found: C, 65.69; H, 5.07: N, 4.20.

[13] Unangst, P. C.; Connor, D. R.; Miller, S. R. *J. Heterocycl. Chem.* **1996**, *33*, 2025−2030.

reaction proceeds even for the sterically hindered *gem*-dimethyl substrate. A slight decrease in the yield of this reaction can be explained by chlorination of the 3-position of the indole as a side reaction.

In conclusion, we have revealed the advantages of this improved procedure for introduction of sulfur at the 3-position of 2-carboxyindoles using a mild method that is tolerant of a wide range of indole and thiol substrates that contain sensitive functionality. This high-yielding reaction provides straightforward access to a wide array of potentially valuable biologically active targets.

Supporting Information Available: Analytical information for entries 2−5 (Table 1) and entries 7−11, 13, and 14 (Table 2) and compounds **7a**,**b** and **8a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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