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A Convenient Modification of the Gassman Oxindole Synthesis

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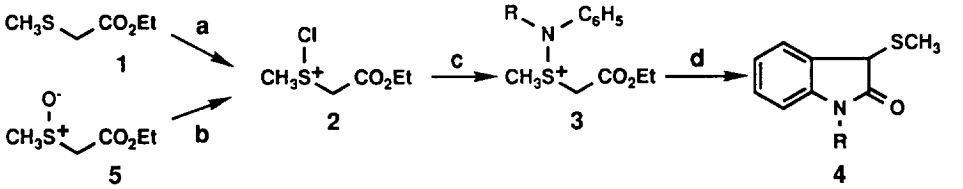
Abstract: *A modification of the Gassman oxindole synthesis is described that proceeds from anilines and ethyl (methylsulfinyl)acetate, using oxalyl chloride to activate the sulfoxide to facilitate the formation of the key N - S bonded intermediate. This procedure is particularly convenient for reactions carried out on smaller scales and for anilines that are susceptible to electrophilic halogenation.* Copyright © 1996 Elsevier Science Ltd

Oxindoles remain an important synthetic target due to the various biological activities associated with some members of this family of compounds, as well as the fact that they are immediate precursors to indoles.[1] Of the various routes to oxindoles which have been reported, most rely on variants of the Friedel - Crafts reaction (Stolle synthesis),[2] while radical, nitrenium ion, organolithium, and photochemical methods have been reported as well.[3] Stolle syntheses are of limited scope because of the harshly acidic conditions required, while the radical, nitrenium ion, organolithium, and photochemical processes are frequently limited by the types of oxindoles that may be prepared as well as compatibility of substrates with the reaction conditions. Syntheses based on the cyclization of *ortho*-aminophenylacetic acid derivatives and the reduction of isatins are limited by the availability of starting materials.[4] The method reported by Gassman and co-workers, which proceeds from an aniline and ethyl (methylthio)acetate via chlorination of the sulfide and subsequent treatment with an aniline and triethylamine, is one of the most generally useful methods in terms of scope, starting material availability, brevity, and reproducibility.[5] We report a modification of this useful reaction that makes it convenient to rapidly carry out this reaction, particularly when multiple and/or smaller scale preparations must be carried out.

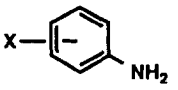
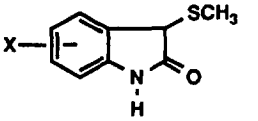
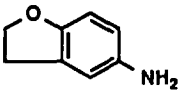
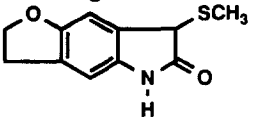
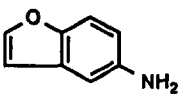
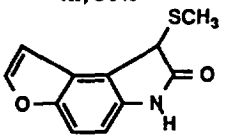
The Gassman oxindole synthesis is believed to proceed from an aniline and ethyl methylthioacetate by rearrangement of the N-S intermediate **3**, which in turn is generated from the chlorosulfonium salt **2**. The key chlorosulfonium salt **2** is typically generated from ethyl methylthioacetate (**1**) and elemental chlorine, which is particularly inconvenient to dispense accurately on a small scale, thus generally requiring the preparation and iodometric titration of a solution of the gas immediately prior to use.[6]



(a) Cl_2, CH_2Cl_2, -78 °C; (b) ClCOCOCl, CH_2Cl_2, -78 °C; (c) C_6H_5NHR, -78 °C; (d) Et_3N, 20 °C then HCl.

Having shown previously that sulfoxides may be the synthetic equivalent of sulfenyl halides in other transformations,[7] we reasoned that the key chlorosulfonium salt **2**, or its equivalent, could easily be obtained from the known sulfoxide **5**.[8] In fact the sulfoxide **5** does undergo oxindole synthesis upon treatment with oxalyl chloride, followed by the addition of the desired aniline, triethylamine, and finally acid cyclization. Besides being much more convenient to manipulate on a small scale, oxindole syntheses with **5** do not afford the dark colors and tars usually encountered with the use of chlorine. Yields are comparable to or in some cases better than those obtained by the use of chlorine or t-butyl hypochlorite (Table 1).[5a]

Table 1

Starting Aniline	Cyclization Product: Yield[a]
	
6a; X = H	**4a**; 63% (65%)
6b; X = 4-CH_3O	**4b**; 50% (53%)
6c; X = 2-CH_3	**4c**; 82% (62%)
6d; X = 4-NO_2	**4d**; 8% (12%)
6e; X = 3,4,5-$(CH_3O)_3$	**4e**; 44% [b]
6f; X = 3-CH_3S	**4f**; 50% [c]
6g; X = 3,5-$(CH_3O)_2$	**4g**; 67% [d]
	
6h[9a]	**4h**; 50% [e,f]
	
6i[9b]	**4i**; 41% [g,h]

[a] All yields represented isolated yields of pure products. Yields obtained by the use of chlorine[5a] are in parentheses. All products gave satisfactory ^1H NMR and mass spectra and were homogeneous by tlc; known products (**4a** - **4d**) had mp in agreement with published values. [b] The aniline was added as a solution in $CHCl_3$. **4e** mp 135 - 137 °C [c] The product was a 1:1 mixture of 3,4-bis- and 3,6-bis-(methylthio)oxindoles. [d] mp 165 - 168 °C. [e] mp 179 - 182 °C. [f] Regiochemical assignment based on ^1H NMR and comparison of desulfurized (RaNi) material to authentic N-ethyl 5,6-dihydrobenzofuran ring-fused analog **7** prepared by another route.[10] [g] mp 171 - 174 °C. [h] Regiochemical assignment based on ^1H NMR non-equivalence to **4h** and comparison of desulfurized (RaNi) material to **7** and desulfurized **4h**.

In addition to being particularly simple to carry out, the reaction is successful for a number of substrates that are particularly sensitive to halogenation and for which the use of the ethyl (methylthio)acetate / chlorine or t-butyl hypochlorite conditions were unsuitable, including the tri- (**6e**) and di- (**6g**) methoxyanilines, the sulfide **6f**, the dihydrobenzofuran **6h**, and especially the benzofuran **6i**. The difference in the regiochemistry of cyclization between the dihydrobenzofuran **6h** and the benzofuran **6i** was striking in that, in each case, none of the alternate regiochemical oxindole was detected in the products **4h** and **4i**.

Attempts to use the crystalline sulfoxide methyl (phenysulfinyl)acetate, to afford 3-(thiophenyl)-oxindoles, were unsuccessful. Starting anilines were recovered in these cases. Likewise, attempts to use trifluoroacetic acid anhydride (TFAA) to activate the sulfoxide (analogously to the use of TFAA in oxidations with DMSO[11]) were also not successful. In this case, the trifluoroacetanilide derived from the anilines **4** was the sole product of the reaction. In addition, the postulated[5a] chlorosulfonium salt **2** may not be an actual intermediate in this reaction sequence, in as much as the use of highly nucleophilic anilines, particularly **6e**, led to a loss of yield due to competing oxanilide formation.

In a typical experiment, 0.85 mL (10 mmol) of oxalyl chloride was dissolved in 25 mL of dry CH_2Cl_2 under N_2 and cooled to -70 °C. A solution of the sulfoxide **5** (1.50 g, 10 mmol) in 5 mL of dry CH_2Cl_2 was added dropwise, and the mixture was stirred at -70 °C for 20 minutes. A solution of redistilled p-anisidine (**6b**, 2.46 g, 20 mmol) in 10 mL of CH_2Cl_2 was added dropwise. The mixture was stirred for 1 h at -70 °C, then a solution of triethylamine (2.24 mL, 16 mmol) was added dropwise. Stirring at -70 °C was continued for 5 min, then the cooling bath was removed. Upon warming to 20 °C, the mixture was treated with 20 mL of water, stirred for 10 min, then filtered and the CH_2Cl_2 layer was separated and evaporated. The residue was taken up in 30 mL of Et_2O and 7.5 mL of 2 M HCl (aq) and stirred for 18 h at 20 °C. The precipitated solid was filtered, washed with water (2 X) and Et_2O (2 X) and dried to afford 0.99 g (50%) of **4b**, mp 146 - 147 °C (lit[5a] mp 149 - 150 °C).

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6. Other halogenating agents that have been used have similar disadvantages: t-butyl hypochlorite[5b, 12] (now only commercially available from ICN and TCI) is of variable quality and must be titrated prior to use. The laboratory preparation of t-butyl hypochlorite is hazardous; see *Org. Syn., Coll. Vol. I V*, p 125; also *Org. Syn., Coll. Vol. V*, p 184. With bromine[5a] many reactions fail entirely. Sulfuryl chloride[13] is frequently contaminated with other chlorides of sulfur, chlorine, and HCl.
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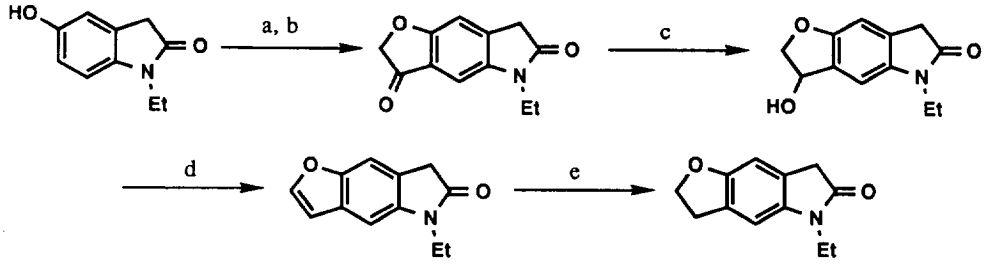
10. A sample of the N-ethyl analog of desulfurized **4h** (**7**) was prepared from N-ethyl-5-hydroxyoxindole[14] by the following sequence of reactions:



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(a) $ClCH_2COCl$, pyr, CH_2Cl_2, 0 °C; (b) $AlCl_3$, 180 °C; (c) $NaBH_4$, EtOH, 20 °C; (d) TFA, MeCN, 20 °C; H_2, 5% Pd/C, EtOH, 45 psig, 25 °C.

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