

Thiomethylation of Indole and Haloindole Zinc Salts

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Abstract: Thiomethylation of indole and haloindoles has been achieved via their zinc salts. This one-pot reaction uses methyl disulfide as electrophile. Isolation of thiomethylated indole products in moderate yields requires the addition of a thiol (e.g., cysteine hydrochloride) during aqueous workup, facilitating the displacement of the thiomethylated product from a water-insoluble zinc salt.

We were interested in a one-pot thiomethylation of indole and haloindoles at C-3. Although previous work has been published regarding the synthesis of (3-thiomethyl)indole¹, to our knowledge, no one-pot synthesis of (3-thiomethyl)indole has been reported. Also, no 3-thiomethylations of any haloindoles have been described in the literature. Based on the reaction summarized in Scheme 1, we were able to achieve the syntheses of 6-bromo-, 6-chloro-, 5-bromo-, and 5-fluoro-(3-thiomethyl)indoles, **2b-e**,² from the zinc salts of their respective indoles, **1b-e**, in moderate yields (Table 1). **1b** was synthesized by a literature method.³

Scheme 1

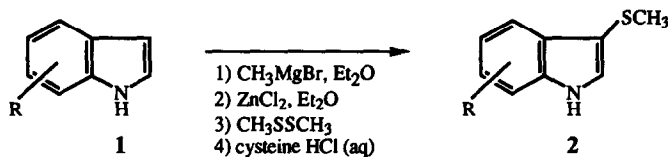


Table 1. Percent Yields of Thiomethylation Products

Reactant	R Substituent	Yield of 2a-e (%)
1a	H	12
1b	6-Br	68
1c	6-Cl	54
1d	5-Br	70
1e	5-F	55.5

In the mechanism of this reaction, we suspect that the zinc ion polarizes the disulfide bond of methyl disulfide, increasing its electrophilicity. According to TLC, only slight conversion to product occurred in the absence of zinc chloride. In the presence of zinc chloride, TLC analysis of the reaction mixtures indicated complete conversion to a single compound, yet in the absence of thiol in the aqueous workup, only low yields of product could be isolated (10% in the case of **2d**). A copious precipitate formed during the reaction was hypothesized to be a zinc salt of the thiomethylated product and thiomethyl anion, and we concluded that adding a high concentration of cysteine hydrochloride to the aqueous workup would compete off the desired product from zinc. However, compound **2a** was not a successful candidate for this thiol-mediated, product displacement; only a 12% yield of **2a** could be obtained. There are at least two possible explanations for the different behavior of **2a**. Compound **2a** may have a larger complexation constant for zinc compared to the other thiomethylindoles containing electron-withdrawing halogens that weaken the electron density at sulfur. Alternatively, the kinetic accessibility of cysteine hydrochloride for compound **2a** may be smaller due to stronger solid-state packing in **2a** than in the other thiomethylindoles that have partially negative halogens causing intermolecular repulsion. The general procedure for the thiomethylation of the indoles is described below.

Thiomethylation of indole and haloindole zinc salts : In a septum-sealed, 10-mL round-bottomed flask, 100-200 mg **1** were dissolved with stirring in 1.0 mL anhydrous ether under dry nitrogen. After connecting the flask by needle to a bubbler, 1.05 eq of 3.0 M methylmagnesium bromide in ether (Aldrich) was injected into the flask. After 15 minutes, 1.05 eq of 1.0 M zinc chloride in ether (Aldrich) was injected into the flask. After another 15 minutes, 3 eq of methyl disulfide (Aldrich) was injected into the flask. The reaction was monitored by quenching aliquots with deionized water, extracting the aqueous mixture with a small portion of ether, and obtaining a TLC of the ether layer (eluent - 1:4 (v/v) ethyl acetate-hexane). After 48-72 hours, all of **1** was converted into a single product, according to TLC. At that time, the reaction was quenched with 5 mL ether and 5 mL deionized water. The product was held in a precipitate. Addition of cysteine hydrochloride (ca. 1 g) dissolved the precipitate. The product was then extracted with 5x5 mL portions of ether. The ether extracts were dried with magnesium sulfate, filtered, and rotary evaporated. The isolated product was dried *in vacuo*.

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REFERENCES AND NOTES

- Tomita, K; Terada, A.; Tachikura, R. *Heterocycles* **1976**, *4*, 729.
- Spectral data for **2a-e**: ¹H-NMR (CDCl₃, TMS reference, 200 MHz) and high resolution MS (ammonia CI); **2a**: 88.20 (br s, 1H, NH), 7.78 (dd, 1H), 7.43-7.18 (m, 4H), 2.45 (s, 3H); M+H: 164.0534 (calculated), 164.0533 (found); **2b**: 88.20 (br s, 1H, NH), 7.59 (d, 1H), 7.52 (d, 1H), 7.31-7.25 (m, 2H), 2.34 (s, 3H); M+·: 240.9561 (calculated), 240.9542 (found); **2c**: 88.38 (br s, 1H, NH), 7.63 (d, 1H), 7.29 (dd, 3H), 2.32 (s, 3H); M+·: 197.0066 (calculated); 197.0076 (found); **2d**: 88.23 (br s, 1H, NH), 7.88 (m, 1H), 7.33-7.21 (m, 3H), 2.34 (s, 3H); M+·: 240.9560 (calculated), 240.9553 (found); **2e**: 88.21 (br s, 1H, NH), 7.43-7.25 (m, 3H), 7.03-6.92 (m, 1H), 2.34 (s, 3H); M+H: 182.0439 (calculated), 182.0433 (found).
- Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1980**, *51*, 5106.

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