GASSMAN INDOLE AND OXINDOLE SYNTHESIS

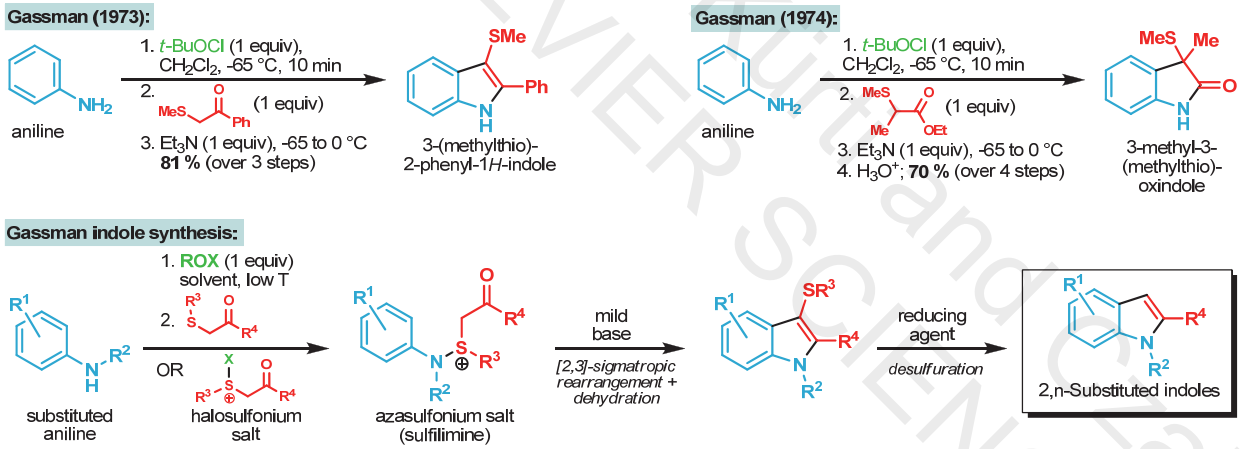
(References are on page XXX)

Importance:

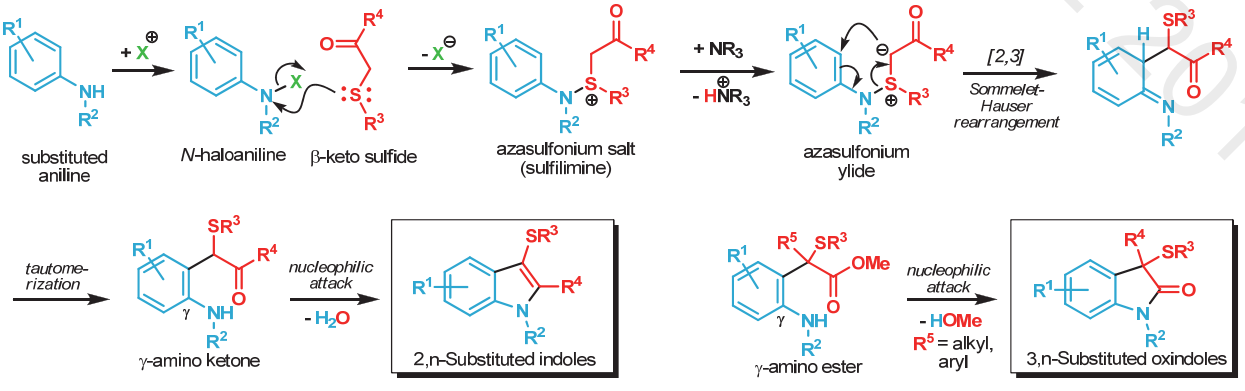
[*Seminal Publications*[1]*; Reviews*[2]*; Modifications & Improvements*[3]*; Theoretical Studies*]

In 1973, P.G. Gassman et al. reported that *N*-halogenated anilines when reacted with α-thiomethyl ketones followed by the addition of a base such Et_3N, led to the formation of 2,3-disubstituted indoles in good to excellent yields.[1a,1b] The thiomethyl (SMe) group in the 3-position could be easily reduced using Raney-Ni and thus 2-substituted indoles were produced. The one-pot conversion of anilines via the corresponding azasulfonium salts (sulfilimines) to 2-substituted indoles using α-thioalkyl ketones (β-keto sulfides) as coupling partners is known as the *Gassman indole synthesis*. When α-thioalkyl esters are used as coupling partners, 3-substituted oxindoles may be prepared; this process is referred to as the Gassman *oxindole synthesis*.[1d]

The general features of these transformations are: **(1)** the aniline substrates, even the relatively highly substituted ones, are usually commercially available or can be readily prepared in a couple of steps from other commercially available materials; **(2)** the β-keto sulfides are also easily accessible from commercial sources or can be prepared from the corresponding α-halo ketones with mercaptides; **(3)** unlike the Fischer indole synthesis that usually requires high temperatures for indole formation, the Gassman indole synthesis takes place at low temperatures (below 0 °C with -65 °C being the ideal T), under mild conditions since no acids or strong bases are used; **(4)** the yields are generally higher than the average yields obtained by the Fischer indole synthesis; **(5)** the initially formed 3-thioalkoxyindoles can be easily desulfurated under Raney nickel reduction and in a similar fashion 3-substituted-3-alkylthiooxindoles give rise to the corresponding 3-substituted indoles; **(6)** a wide range of electron-donating and electron-withdrawing substituents are tolerated (from alkyl all the way to nitro) on the aniline substrate, however, one limitation is that cation-stabilizing groups such as alkoxy groups (e.g., OMe) may not be present at the *ortho* or *para* positions, since the corresponding *N*-chloro-anisidines are unstable even at -78 °C; **(7)** the Gassman method is applicable to both *ortho*- and *para*-substituted anilines: the former gives rise to 2,7-disubstituted indoles, while the latter affords 2,5-disubstituted indoles; **(8)** *N*-substituted indoles can also be accessed by starting from *N*-alkyl or *N*-arylanilines; **(9)** *meta*-substituted anilines give rise to mixtures of 2,4- and 2,6-disubstituted indoles; **(10)** if the *meta* substituent is strongly electron-withdrawing (e.g., NO_2), the only product is the 2,6-disubstituted indole; **(11)** the only disadvantage of the original procedure is the use of the halogen source, most often a hypohalite (ROX), which may not be compatible with electron-rich functional groups such as alkenes; **(12)** in a modified procedure a chlorine-sulfide complex[3a,3b] (halosulfonium halide) is formed prior to reaction with the aniline thus even strongly electron-rich anilines (e.g., anisidines) may be converted to indoles in good yields without the formation of electrophilic halogenation (S_EAr) side products.



Mechanism:[1c,1d]

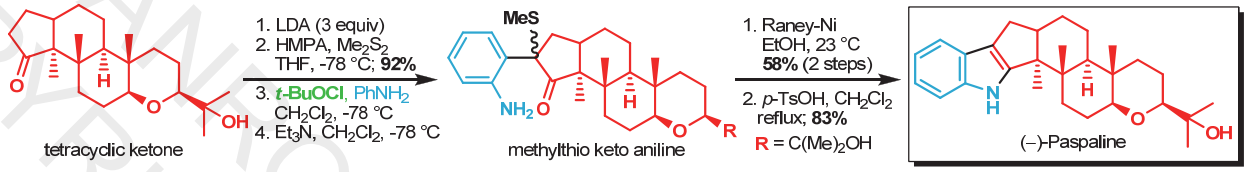


GASSMAN INDOLE AND OXINDOLE SYNTHESIS

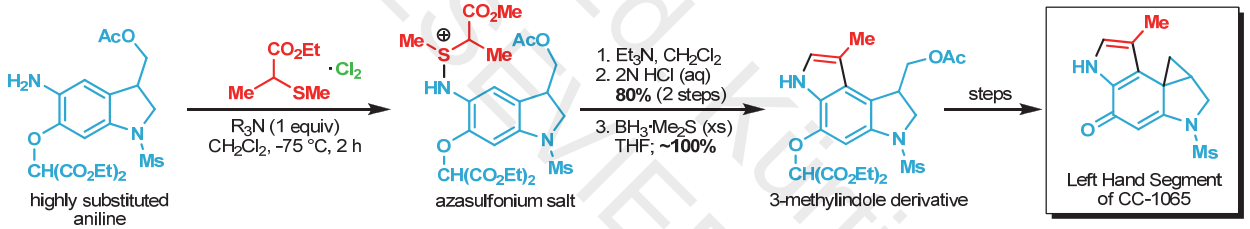
(Sample experimental procedure is on page XXX)

Synthetic Applications:

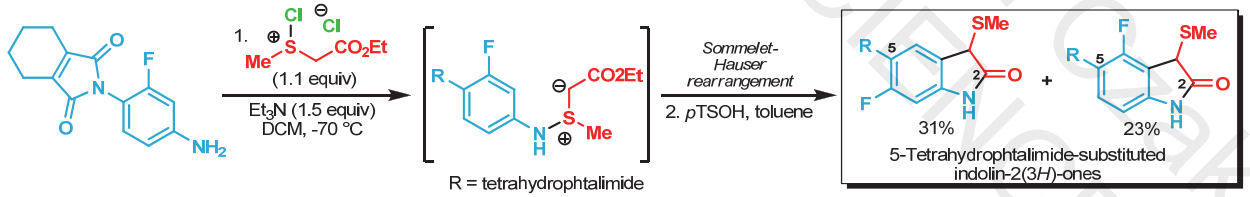
(1) The most complex synthetic example in which the *Gassman indole protocol* was used as a key step is taken from the total synthesis of (–)-paspaline by A.B. Smith and co-workers.[4] The synthetic sequence commenced with an advanced tetracyclic ketone that was first treated with LDA. The resulting lithium enolate was then sulfenylated with Me_2S_2, which gave rise to a 1:1 mixture of methylthio ketone diastereomers (not shown). Next, *N*-chloroaniline was generated *in situ* at -78 °C and allowed to react with the diastereomeric mixture of methylthio ketones. Treatment of the resulting azasulfonium salt with triethylamine afforded a 16:1 mixture of epimeric methylthio keto anilines. Removal of the methylthio group was achieved by reduction with excess Raney nickel to furnish a single compound which underwent facile indole formation upon treatment with *p*-TsOH in dichloromethane at reflux to furnish (–)-paspaline in 83% yield.



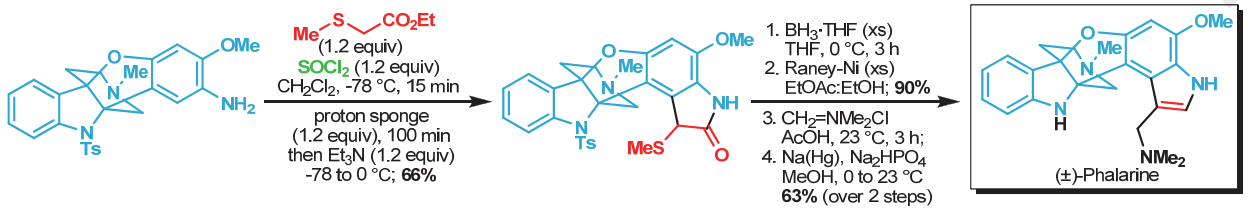
(2) The left hand segment of the highly cytotoxic agent CC-1065 was prepared by W. Wieranga using the *Gassman oxindole synthesis* (essentially the sulfonium ylide version of the *Sommelet-Hauser rearrangement*).[5] The highly substituted aniline was first treated with the chlorine complex of ethyl α-(mercaptomethyl)propionate and a very hindered tertiary amine (R_3N = 1,8-bis(dimethylamino)-naphthalene or isopentyldiisopropyl-amine). The resulting azasulfonium salt was then treated with triethylamine to induce the *[2,3]-sigmatropic rearrangement*; acidic workup gave rise to oxindole as a mixture of diastereomers. Attemps to reduce the oxindole with $LiAlH_4$ to the corresponding indoline proved unsuccessful. However, reduction with borane furnished the 3-methyl substituted indole derivative directly in nearly quantitative yield, presumably due to the presence of the alkylthio substituent which is eliminated in the process. Three additional steps were necessary to prepare the desired left hand segment of CC-1065.



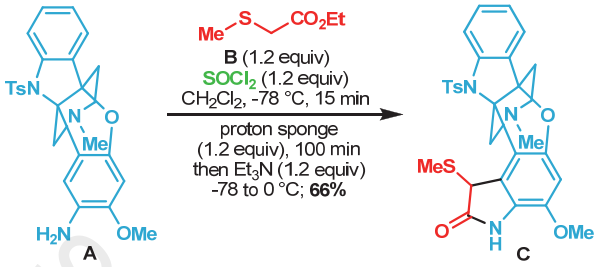
(3) Novel regioisomeric tetrahydrophthalimide-substituted indoline-2(3*H*)-ones were prepared as potential herbicides by G.M. Karp et al. utilizing the *Gassman oxindole synthesis*.[6] The unsymmetrical aniline substrate was treated with the chlorosulfonium salt of ethyl (methylthio)acetate and triethylamine at low temperature. The resulting regioisomeric amino esters were cyclized to the regioisomeric indoline-2(3*H*)-ones that were separated by column chromatography.



(4) The first total synthesis of the potentially neurotoxic alkaloid (±)-phalarine was accomplished by S.J. Danishefsky and co-workers.[7] The researchers planned to install the 3,7-disubstituted indole moiety of the molecule at the end of the synthetic sequence. However, indole formation using the *Fischer indole synthesis* was low yielding since a number of side products were formed due to the presence of the *ortho*-methoxy group. Eventually the indole moiety was successfully formed via the *Gassman oxindole synthesis*. Four more steps were needed to complete the total synthesis of (±)-phalarine.



Gassmann Indole and Oxindole Synthesis.....xxx



Ref: Li, C., Chan, C., Heimann, A. C. & Danishefsky, S. J. Total synthesis of phalarine. *Angew. Chem., Int. Ed.* **2007**, 46, 1448-1450.

Procedure: 12 mL CH_2Cl_2 was cooled to -78 °C under Ar. Ethyl (methylthio)acetate **B** (300 µL, 2.34 mmol, 1.2 equiv) was added by syringe, followed by sulfuryl chloride (189 µL, 2.34 mmol, 1.2 equiv), and the resulting mixture was stirred for 15 min. A solution of **A** (930 mg, 1.95 mmol) and proton-sponge (500 mg, 2.34 mmol, 1.2 equiv) in CH_2Cl_2 (6 mL) was added over 20 min. After the reaction was stirred for 100 min, a solution of Et_3N (326 µL, 2.34 mmol, 1.2 equiv) in CH_2Cl_2 (5 mL) was added dropwise and the reaction was allowed to warm to rt. The mixture was washed with H_2O. The combined aqueous layers were back-extracted with CH_2Cl_2. The organic layers were combined, dried with Na2SO4, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (40% of EtOAc/hexane to pure EtOAc) to provide 725 mg (1.29 mmol, 66%) α-SMe oxindole **C** (Rf (EtOAc with 1%NEt_3) = 0.67) as a slightly reddish solid and 140 mg of recovered starting material **A** (Rf (EtOAc with 1% NEt_3) = 0.22) (78% brsm).

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