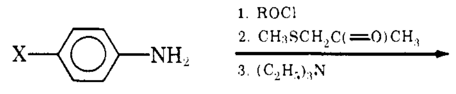
A Simple Method for the Conversion of Anilines into 2-Substituted Indoles

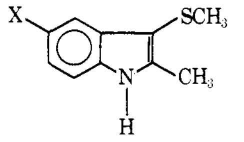
Sir:

In the preceding communication,[1] Gassman and Gruetzmacher have described a general procedure for the stereospecific alkylation of aromatic amines. We now wish to report the development of a new, general synthetic procedure for the synthesis of indoles,[2] which is based on a modification of this alkylation process.

In a general procedure, 1 equiv of a suitable halogenating agent[3] was added to a vigorously stirred solution[4] of 1 equiv of an aniline, of general formula **1**, at −65°[5] and the reaction was stirred for 5–10 min after the addition was completed. An equivalent of methylthio-2-propanone[6] was added at −65°[5] and the reaction mixture was stirred for an additional hour. An equivalent of base (triethylamine worked quite well) was added at −65°,[5] the cooling bath was removed, and the reaction mixture was stirred and allowed to warm to room temperature. The indole derivatives, **2**, were then isolated by standard techniques. As shown below, the yields of substituted indoles obtained through this process are quite good. In all cases, the thiomethyl group could be removed in high yield (>70%) *via* reduction with Raney nickel at 25° to give the corresponding 2,5-disubstituted indole.[7]

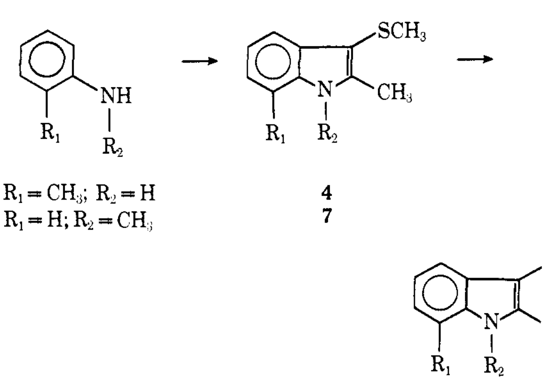


1a, X = OC(=O)CH_3
1b, X = CH_3
1c, X = H
1d, X = Cl
1e, X = $CO_2C_2H_5$



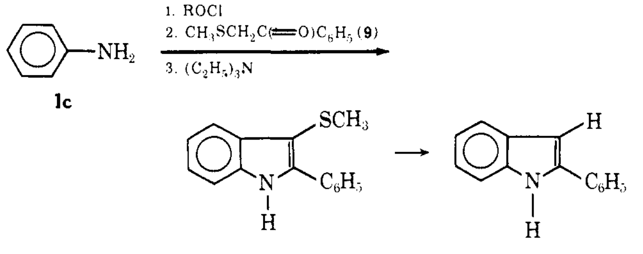
	% yield
2a	68
2b	60
2c	69
2d	72
2e	58

The process is quite general. Utilizing the conditions described above, *o*-toluidine (**3**) was converted into **4** (72% yield), and then **4** was reduced to **5** (73% yield). Thus, 2,7-disubstituted indoles can be readily prepared from ortho-substituted anilines. Our procedure can also be used to prepare 1-substituted indoles. Under our general reaction conditions *N*-methylaniline (**6**) gave **7** (54% based on unrecovered **6**), which on Raney nickel reduction gave the 1,2-disubstituted indole **8** (76% yield).



3, $R_1 = CH_3$; $R_2 = H$ → **4** → **5**
6, $R_1 = H$; $R_2 = CH_3$ → **7** → **8**

In principle, a wide variety of substituents should be able to be placed at the 2 position of the indole nucleus by varying the nature of the keto sulfide used in the reaction. When methyl phenacyl sulfide (**9**)[8] was used with aniline (**1c**), we obtained an 81% yield of **10**. Raney nickel reduction of **10** gave **11** in 74% yield.



1c **10** **11**

The examples cited above illustrate some of the versatility of our new approach to indole synthesis. As shown, the use of keto sulfides with aromatic amines provides a simple route to a broad category of 2-substituted indoles. In order to further evaluate the utility of our procedure, we need to compare it to the presently preferred methods of indole synthesis. The Fischer indole synthesis[9,10] has received the most widespread use because it, when coupled with the Japp–Klingemann reaction,[11] has been the most versatile and widely applicable method of obtaining indoles up to this time. Our process has certain advantages over the Fischer method. First, the starting materials for our method are in general quite readily available and, for the most part, quite inexpensive. For substitution in the 4, 5, 6, or 7 positions the Fischer indole synthesis requires the appropriately substituted phenylhydrazine.

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(1) P. G. Gassman and G. Gruetzmacher, *J. Amer. Chem. Soc.*, **95**, 588 (1973).

(2) For detailed discussions of the presently known methods of indole synthesis see R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, and R. K. Brown in "Indoles," Part I, W. J. Houlihan, Ed., Wiley-Interscience, New York, N. Y., 1972.

(3) Any active chlorine source can be used in this procedure when appropriate experimental modifications are made. In practice, we found that of the various hypohalites, which can be used, *tert*-butyl hypochlorite was most convenient on a laboratory scale.

(4) The reaction sequence does not appear to be very solvent dependent. Of the various solvents used, we have found methylene chloride to be most convenient.

(5) This reaction can be run over a wide range of temperatures. In general, yields tended to maximize at *ca.* −65°. The extent of the temperature range is a function of the substituents on the aniline.

(6) C. K. Bradsher, F. C. Brown, and R. J. Grantham, *J. Amer. Chem. Soc.*, 76, 114 (1954).

(7) Satisfactory elemental analyses have been obtained on all new compounds. Infrared and nmr spectra of all new compounds have also been consistent with the assigned structures. The desulfurization products 2-methylindole and 2,5-dimethylindole were identified *via* comparison with authentic samples.

(8) V. Prelog, V. Hahn, H. Brauchli, and H. C. Beyerman, *Helv. Chim. Acta*, 27, 1209 (1944).

(9) E. Fischer and F. Jourdan, *Chem. Ber.*, **16**, 2241 (1883); E. Fischer and O. Hess, *ibid.*, **17**, 559 (1884); E. Fischer, *Justus Liebigs Ann. Chem.*, **236**, 126 (1886).

(10) For a recent review see B. Robinson, *Chem. Rev.*, **69**, 227 (1969).

(11) F. R. Japp and F. Klingemann, *Chem. Ber.*, **20**, 2942, 3284, 3398 (1887). For a review see R. R. Phillips, *Org. React.*, **10**, 143 (1959).

These often require tedious synthesis. By comparison, an unusually large variety of ring-substituted anilines are commercially available for use in our procedure. For the synthesis of 1-substituted indoles the Fischer method requires the availability of the appropriate 1,1-disubstituted hydrazine. These are difficult to prepare. Our method requires the appropriate N-substituted aniline. Again, many such secondary anilines are common catalog chemicals. The keto sulfides are also easily obtained. Many are commercially available. Those which cannot be purchased are easily synthesized from the appropriate halo ketone and methyl mercaptide.

Another advantage of our process is the unusually mild conditions involved in the formation of the indole nucleus. All of the steps involved can be run below 0°. No acid or strong base is involved. Hence, our method is applicable to the preparation of indole derivatives with functionality which would be sensitive to elevated temperatures, acids, or strong base.

Finally, the yields obtained in our synthesis of the indole nucleus appear superior to the average yields obtained by the Fischer method.

Acknowledgment. We are indebted to the National Cancer Institute of the Public Health Service for a grant which partially supported this investigation.

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(12) Fellow of the Netherlands Organization for the Advancement of Pure Research (Z.W.O.), 1972–1973.

Paul G. Gassman,* T. J. van Bergen[12]
Department of Chemistry, The Ohio State University
Columbus, Ohio 43210

Received October 4, 1972

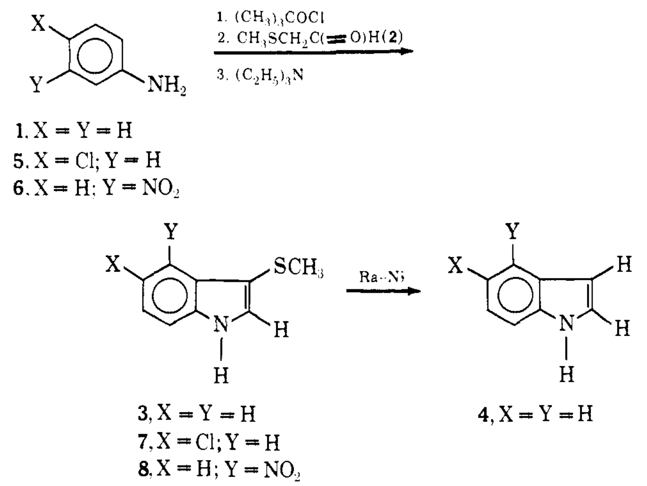
Use of Methylthioacetaldehyde in the Synthesis of Indole and Its Derivatives

Sir:

In the preceding communication, we have described a general method for the synthesis of 2-alkyl- and 2-arylindoles from anilines and keto sulfides.[1] We now wish to report a modification of this synthetic method, which permits the synthesis of a variety of indoles unsubstituted in the 2 position. We also wish to present what we believe to be the mechanism of this very useful and versatile method for the synthesis of indoles.

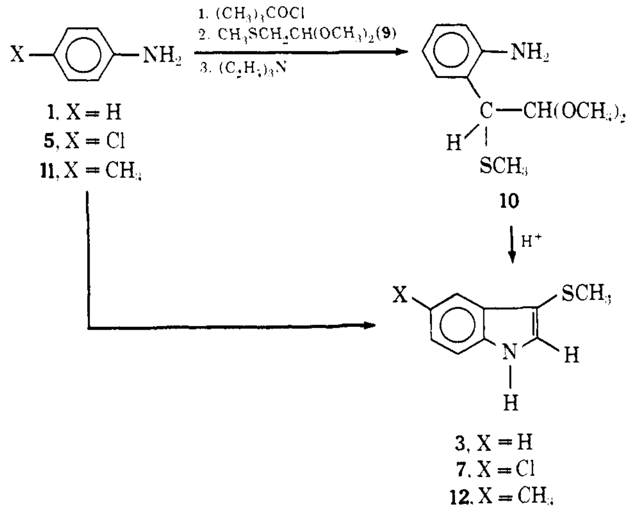
When aniline (**1**) was treated with 1 equiv of *tert*-butyl hypochlorite in methylene chloride solution at −65°, followed by addition of methylthioacetaldehyde (**2**)[2] at −65° and treatment with triethylamine, we obtained **3** in 30% yield (Scheme I). Raney nickel reduction of **3** at room temperature gave an 82% yield of indole (**4**). Similar treatment of *p*-chloroaniline (**5**) and *m*-nitroaniline (**6**) gave the indoles **7** and **8**, in 35 and 38% yields, respectively. In the case of **7**, the yield was 50% when unreacted *p*-chloroaniline was taken into consideration.

Scheme I



From mechanistic considerations (*vide post*), we felt that the use of **9**,[2] the dimethyl ketal of **2**, might provide some advantages over the use of **2**. When **1** was treated with *tert*-butyl hypochlorite under the standard conditions, followed by the addition of 1 equiv of **9**, and subsequent addition of triethylamine, we were able to isolate **10** in 57% yield (Scheme II). The structure of **10** was established on the basis of elemental analysis,[3] ir spectroscopy, and its nmr spectrum, which showed peaks at τ (CCl$_4$) 2.82–3.67 (4 H, aromatic protons), 5.39 (1 H, d, J = 7 Hz), 6.02 (1 H, d, J = 7 Hz), 6.17 (2 H, br s, NH$_2$), 6.65 and 6.88 (3 H, s, diastereomeric OCH$_3$), and 8.22 (3 H, s, SCH$_3$). Treatment of an ethereal solution of **10** with a 0.5 N aqueous solution of hydrochloric acid gave a 97% yield of **3** for an overall yield of 55% of **3** from **1**. If, instead of isolating **10**, the crude reaction mixture was treated with acid, we obtained an overall yield of 45% of **3**. Utilizing this procedure (no isolation of the intermediate ketal) with *p*-toluidine (**11**) and *p*-chloroaniline (**5**) gave **12** and **7** in 39 and 23% yields, respectively.

Scheme II



The general mechanism for the formation of indoles from anilines is depicted in Scheme III. As we have previously shown,[4,5] anilines (**13**) react readily with

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[1] P. G. Gassman and T. J. van Bergen, *J. Amer. Chem. Soc.*, **95**, 590(1973).

[2] For the preparation of **2** and **9** see E. H. Wick, T. Yamanishi, H. C. Wertheimer, Y. E. Hoff, B. E. Proctor, and S. A. Goldblith, *J. Agr. Food Chem.*, **9**, 289 (1961). A slight modification of the literature procedure allowed us to improve the yield of **2** from the 21% reported to 67%.

[3] Satisfactory elemental analyses have been obtained on all new compounds. Infrared and nmr spectra of all new compounds have also been consistent with the assigned structures. The structure of **4** was authenticated by comparison with a known sample.

[4] P. G. Gassman, G. A. Campbell, and R. C. Frederick, *J. Amer. Chem. Soc.*, **94**, 3884 (1972); P. G. Gassman and G. A. Campbell, *ibid.*, **94**, 3891 (1972); see also P. Haberfield and D. Paul, *ibid.*, **87**, 5502(1965).

[5] P. G. Gassman and G. Gruetzmacher, *ibid.*, **95**, 588 (1973).