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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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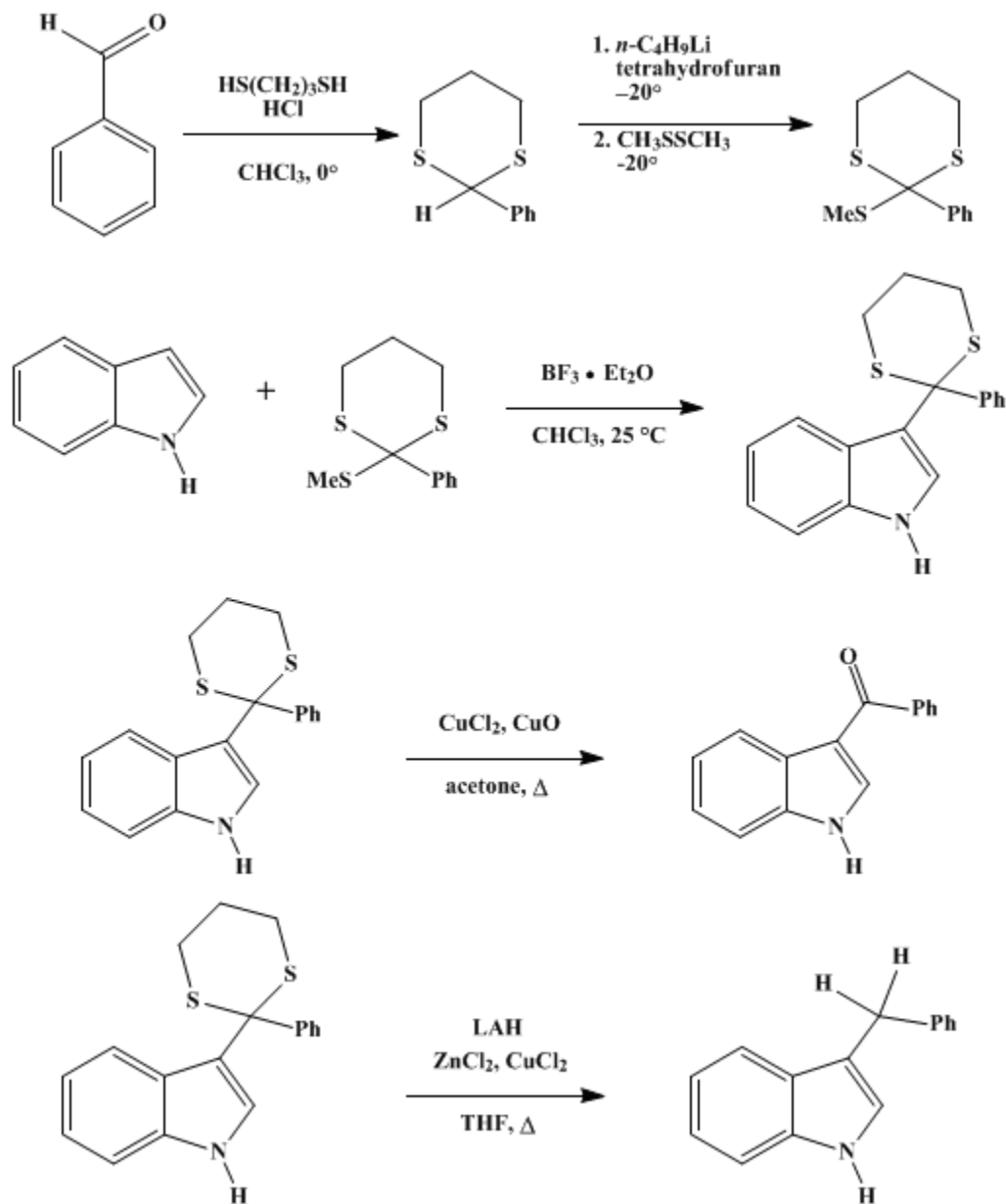
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Organic Syntheses, Coll. Vol. 6, p.109 (1988); Vol. 56, p.8 (1977).

3-ALKYLATED AND 3-ACYLATED INDOLES FROM A COMMON PRECURSOR: 3-BENZYLINDOLE AND 3-BENZOYLINDOLE

[1*H*-Indole, 3-(phenylmethyl)- and Methanone, 1*H*-indole-3-ylphenyl-]



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Checked by M. Cushman and G. Büchi.

1. Procedure

Caution! The following reactions should be conducted in a well-ventilated hood, since in each step evil-smelling sulfur compounds are either used as starting materials or generated during the reaction.

A. *2-Phenyl-1,3-dithiane*. A 100 ml., two-necked, round-bottomed flask fitted with a gas-inlet tube and a drying tube containing glass wool is charged with 5.52 g. (5.28 ml., 0.0521 mole) of *benzaldehyde*, 5.6 g. (5.2 ml., 0.052 mole) of *1,3-propanedithiol*, and 30 ml. of *chloroform* (Note 1). The flask is immersed in an ice bath, and a slow stream of *hydrogen chloride* gas is bubbled through the solution. When saturated (after *ca.* 5 minutes), the reaction mixture is left at room temperature for 30 minutes, then evaporated at reduced pressure. The oily residue (Note 2) is taken up in 50 ml. of *methanol* and vigorously agitated to induce crystallization. The crystals are collected by filtration, washed with ligroin, and air dried. By condensing the mother liquors, two more crops may be obtained, giving a total of 9.5–9.7 g. (93–95%) of *2-phenyl-1,3-dithiane*, m.p. 69–70° (Note 3).

B. *2-Methylthio-2-phenyl-1,3-dithiane*. A 2-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a gas inlet connected to a nitrogen source, and a pressure-equalizing dropping funnel. The apparatus is maintained under a positive pressure of *nitrogen* and carefully protected from moisture throughout the ensuing reaction. The flask is charged with 37.2 g. (0.190 mole) of *2-phenyl-1,3-dithiane* and 600 ml. of anhydrous *tetrahydrofuran*, and 0.228 mole of *n-butyllithium* in *hexane* (Note 4) is placed in the funnel. With stirring, the flask is cooled with a –20° bath, and the *n-butyllithium* solution is run into the flask over a 10-minute period. Stirring and cooling are continued for 2 hours, after which a solution of 32.2 g. (30.4 ml., 0.342 mole) of *dimethyl disulfide* (Note 5) in 50 ml. of anhydrous *tetrahydrofuran* is added over a 10-minute period. The cooling bath is then removed, and as the solution is stirred at room temperature a fine, white precipitate forms.

When the reaction mixture has been at room temperature for 90 minutes, 300 ml. of saturated aqueous *sodium chloride* is added slowly, followed by 500 ml. of *chloroform*. The resulting aqueous layer is separated and washed with three 100-ml. portions of *chloroform*, and the combined *chloroform* solutions are dried with *sodium sulfate* and decolorized with *activated carbon*. Removal of *chloroform* with a rotary evaporator leaves an oily residue, which is readily crystallized from 100 ml. of *methanol*. The colorless crystals are collected by filtration and washed with petroleum ether, giving 33.5–35.3 g. (72–77%) of *2-methylthio-2-phenyl-1,3-dithiane*, m.p. 76–78°. A second crop of crystalline product may be obtained from the mother liquors.

C. *3-(2-Phenyl-1,3-dithian-2-yl)-1H-indole*. A solution of 24.2 g. (0.102 mole) of *2-methylthio-2-phenyl-1,3-dithiane* and 5.86 g. (0.0501 mole) of *indole* in 600 ml. of *chloroform* is placed in a 2-l., three-necked flask fitted with a mechanical stirrer and a 100-ml., pressure-equalizing dropping funnel. The reaction mixture is stirred vigorously as a solution of 25 ml. (about 0.2 mole) of *boron trifluoride diethyl etherate* (Note 6) in 50 ml. of *chloroform* is added over 10 minutes. An orange–brown, resinous precipitate forms as the slightly exothermic reaction proceeds. After an additional 10 minutes of stirring, a solution of 5.86 g. (0.0501 mole) of *indole* in 50 ml. of *chloroform* is added in one portion.

Stirring is continued for 2 hours at room temperature, and *methanol* is added until a clear solution is obtained (*ca.* 10 ml. of *methanol* is required, and some heat is generated). When the solution has cooled, it is washed successively with 200 ml. of aqueous 2 *N* *potassium carbonate* and 200 ml. of water. The aqueous phases are combined, washed with three 100-ml. portions of *chloroform*, and discarded. The organic phases are combined, dried over *sodium sulfate*, and decolorized with *activated carbon*. Concentration of the *chloroform* solution obtained provides three crops of pale yellow crystals, which are washed with 30% *hexane* in *chloroform* and dried for 2 hours at 80°/0.1 mm, yielding 22.3–25.4 g. (72–81%) of *3-(2-phenyl-1,3-dithian-2-yl)-1H-indole*, m.p. 167–169° (Note 7). This material requires no further purification for use in Parts D or E.

D. *3-Benzoylindole*. A 100-ml., three-necked flask fitted with a magnetic stirring bar, a condenser, and a pressure-equalizing dropping funnel is charged with 0.48 g. (0.0060 mole) of *copper(II) oxide*, 1.61 g. (0.0120 mole) of anhydrous *copper(II) chloride* (Note 8), and 40 ml. of *acetone*. The resulting suspension is brought to reflux with vigorous stirring, and a solution of 1.55 g. (0.00508 mole) of *3-(2-phenyl-1,3-dithian-2-yl)-1H-indole* in 9 ml. of *acetone* and 1 ml. of *N,N-dimethylformamide* is added over 5 minutes. Reflux temperatures are maintained for 90 minutes, during which time the reaction mixture gradually turns yellow, then the mixture is cooled and filtered. The insoluble material is washed with three 20-ml. portions of hot 10% *ethanol* in *dichloromethane*, and the combined organic solutions are washed with 50 ml. of aqueous 2 *N* *sodium carbonate* (Note 9), dried over *sodium sulfate*, and filtered. Concentration of the filtrate to a small volume under reduced pressure gives a residue which

gradually deposits crystals. Filtration provides 0.94–0.97 g. (85–88%) of pure 3-benzoylindole, m.p. 238–240°.

E. *3-Benzylindole*. A suspension of 1.34 g. (0.0100 mole) of anhydrous copper(II) chloride (Note 8) and 2.72 g. (0.0200 mole) of anhydrous zinc chloride (Note 10) in 150 ml. of anhydrous tetrahydrofuran is prepared in a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer and a condenser connected to a nitrogen source. This mixture is stirred at room temperature and maintained under a nitrogen atmosphere while 3.04 g. (0.0800 mole) of lithium aluminum hydride is added cautiously in small portions (Note 11). The resulting exothermic reaction gives a black precipitate, which is stirred at room temperature for 45 minutes before 1.55 g. (0.00508 mole) of 3-(2-phenyl-1,3-dithian-2-yl)-1*H*-indole is added. Stirring is continued as the mixture is refluxed for 1 hour, cooled to room temperature, and quenched by careful dropwise addition of 10 ml. of water. The resulting slurry is diluted with 100 ml. of dichloromethane and filtered to remove inorganic salts, which are washed by digesting with three 50-ml. portions of refluxing dichloromethane. The combined filtrates are then washed with a solution of 4.0 g. (0.012 mole) of mercury(II) acetate in 100 ml. of water, dried over sodium sulfate, filtered, and concentrated on a rotary evaporator, leaving about 1.1 g. of a yellow crystalline residue. Bulb-to-bulb distillation at 145–155° (0.1 mm.) yields 0.74–0.85 g. (72–82%) of practically pure 3-benzylindole as pale yellow crystals, m.p. 102–105° (Note 12).

2. Notes

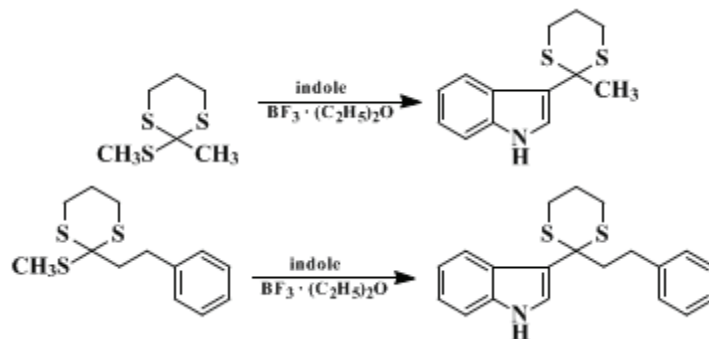
1. benzaldehyde and 1,3-propanedithiol were purchased from the Aldrich Chemical Company, Inc., and used without further purification. Exclusion of moisture during the reaction is advantageous but not essential.
2. The checkers obtained a crystalline residue, which was triturated with 10 ml. of methanol and filtered.
3. The method used is quite general for substituted 1,3-dithianes.² A different method is required for the preparation of 1,3-dithiane itself [*Org. Synth., Coll. Vol. 6*, 556 (1988)].
4. The volume of solution required will depend on the concentration of *n*-butyllithium, which should be determined by titration prior to use. A convenient procedure utilizes 1,10-phenanthroline as an indicator; titration to the colorless end point with 2-butanol³ in xylene gives organolithium concentration directly.⁴ A method for transferring large volumes of *n*-butyllithium solution is outlined in [*Org. Synth., Coll. Vol. 6*, 979 (1988)].
5. Dimethyl disulfide was obtained from the Aldrich Chemical Company, Inc., and used without further purification. The molar ratio used is the same as that in the original reference.⁵
6. Boron trifluoride etherate was purchased from either Fluka AG, Switzerland or Aldrich Chemical Company, Inc. The checkers distilled the commercial material from calcium hydride immediately prior to use.⁶
7. ¹H NMR (CDCl₃), δ (multiplicity, coupling constant *J* in Hz., number of protons): 1.5–2.2 (m, 2H), 2.7–3.0 (m, 4H), 7.0 (d, *J* = 2.5, 1H), 7.1–7.5 (m, 6H), 7.7–8.2 (m, 4H). A sample recrystallized from methanol–chloroform melted at 183–185°. The submitters also obtained pure product, m.p. 181–183°, after chromatography on basic alumina with 20% petroleum ether in dichloromethane as eluent.
8. Anhydrous copper(II) chloride was prepared by heating the dihydrate at 110° overnight.
9. This extraction must be performed gently, since violent agitation will give an emulsion.
10. Reagent grade anhydrous zinc chloride was obtained from Merck & Company, Inc.
11. Lithium aluminum hydride was obtained from Fluka AG or from Ventron Corporation. One convenient technique for the addition is to weigh the reagent into an Erlenmeyer flask, which is then connected to the reaction flask by a short piece of Gooch tubing. In this way the solid can be added in portions without exposing it to the atmosphere.
12. Various melting points are reported in the literature for 3-benzylindole: 96–98°,⁷ 103°, and 107°.⁸

3. Discussion

There are other convenient methods for the preparation of 3-benzylindole^{7,8} and 3-benzoylindole.⁹ The present procedure, however, has two useful elements of flexibility: it produces both 3-alkyl- and 3-acylindoles from a single precursor, and it tolerates the presence of a wide variety of substituents.

The pivotal step in this sequence is an electrophilic substitution on **indole**. Although the use of 1,3-dithian-2-yl carbanions is well documented, it has been shown only recently that 1,3-dithian-2-yl carbenium ions can be used in a Friedel–Crafts type reaction. This was accomplished initially using 2-methoxy-1,3-dithiane or 2-methoxy-1,3-dithiolane and titanium tetrachloride as the Lewis acid catalyst.¹⁰ 2-Substituted lysergic acid derivatives and 3-substituted indoles have been prepared under these conditions, but the method is limited in scope by the difficulties of preparing substituted 2-methoxy-1,3-dithianes. 1,3-Dithian-2-yl carbenium ions have also been prepared by protonation of ketene dithioacetals with trifluoroacetic acid,¹¹ but this reaction cannot be used to introduce 1,3-dithiane moieties into **indole**.

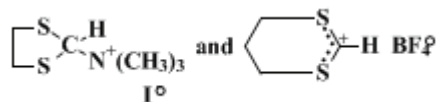
The procedure described herein is fairly general for indoles, and since 2-methylthio-1,3-dithianes are readily available,^{3,5} it should prove versatile. Two further examples are as follows:



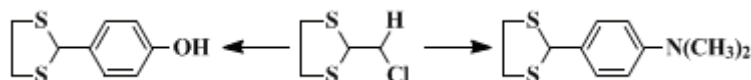
In attempting to extend the method to other activated aromatics, it was found that pyrroles give mixtures of 2- and 3-substituted products, and that **naphthol** ethers and **benzo[b]thiophene** fail to react.

The hydrolytic step (Part D) uses conditions described by Narasaka, Sakashita, and Mukaiyama.¹² It was necessary to modify the original stoichiometry, since the recommended molar ratio of substrate: **copper(II) chloride**: **copper(II) oxide** (1:2:4) gave only a 57% yield of **3-benzoylindole**. The more generally known mercuric oxide-mercuric chloride hydrolysis² may also be used, and in the present case it gives a yield of about 90%. The reductive desulfurization of Part E, also based on the work of Mukaiyama,¹³ is clearly superior to **Raney nickel** desulfurization, which gives only 35–45% of **3-benzylindole**.

Some new reagents of the same general type, leading to intermediate carbocations of dithians, have been reported in the literature recently. Hiratani, Nakai, and Okawara synthesized 1,3-dithian-2-yltrimethylammonium iodide.¹⁴ Corey and Walinsky¹⁵ applied 1,3-dithian-2-yl fluoroborate, prepared by hydride ion exchange from 1,3-dithiane and **trityl fluoroborate**,¹⁶ to a new kind of electrophilic reaction for the preparation of cyclopentane derivatives.



Further, substantial progress leading to a generally applicable method is shown by the preparation of **2-chloro-1,3-dithiane** and its application in electrophilic substitution reactions with reactive aromatic molecules like **phenol** and ***N,N*-dimethylaniline**.¹⁷



So far, however, no reagent of the dithianylcarbocation type has been found which allows electrophilic substitution reactions with unactivated aromatic molecules such as **benzene**.

References and Notes

1. Sandoz Ltd., Pharmaceutical Division, Preclinical Research, Basel, Switzerland.
 2. D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **6**, 442 (1967); D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).
 3. For a warning concerning 2-butanol, see *Chem. Eng. News*, **59**, (19), 3 (1981).
 4. S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
 5. R. A. Ellison, W. D. Woessner, and C. C. Williams, *J. Org. Chem.*, **37**, 2757 (1972).
 6. G. Zweifel and H. C. Brown, *Org. React.*, **13**, 28 (1963).
 7. H. Plieninger, *Chem. Ber.*, **87**, 127 (1954).
 8. R. Cornforth and R. Robinson, *J. Chem. Soc.*, 680 (1942).
 9. W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).
 10. P. Stütz and P. A. Stadler, *Helv. Chim. Acta*, **55**, 75 (1972).
 11. F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 1926 (1972).
 12. K. Narasaka, T. Sakashita, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **45**, 37 (1972).
 13. T. Mukaiyama, *Int. J. Sulfur Chem.*, **7**, 173 (1972).
 14. K. Hiratani, T. Nakai, and M. Okawara, *Bull. Chem. Soc. Jpn.*, **46**, 3510 (1973).
 15. E. J. Corey and S. W. Walinsky, *J. Am. Chem. Soc.*, **94**, 8932 (1972).
 16. H. J. Dauben, L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, **25**, 1442 (1960).
 17. K. Arai and M. Oki, *Tetrahedron Lett.*, **1975**, 2183; K. Arai and M. Oki, *Bull. Chem. Soc. Jpn.*, **49**, 553 (1976); C. G. Kruse, N. L. J. M. Broekhof, A. Wijsman, and A. van der Gen, *Tetrahedron Lett.*, **1977**, 885; C. G. Kruse, A. Wijsman, and A. van der Gen, *J. Org. Chem.*, **44**, 1847 (1979).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

petroleum ether

2-methoxy-1,3-dithianes

2-methylthio-1,3-dithianes

mercuric oxide-mercuric chloride

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

chloroform (67-66-3)

phenol (108-95-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

naphthol (90-15-3)

sulfur (7704-34-9)

mercury(II) acetate (1600-27-7)

benzaldehyde (100-52-7)

Raney nickel (7440-02-0)

acetone (67-64-1)

carbon,
activated carbon (7782-42-5)

zinc chloride (7646-85-7)

copper(II) chloride (7758-89-6)

xylene (106-42-3)

N,N-dimethylaniline (121-69-7)

copper(II) oxide (1317-38-0)

dichloromethane (75-09-2)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

Indole (120-72-9)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

boron trifluoride etherate,
boron trifluoride diethyl etherate (109-63-7)

calcium hydride (7789-78-8)

trifluoroacetic acid (76-05-1)

dimethyl disulfide (624-92-0)

benzo[b]thiophene (95-15-8)

2-Butanol (78-92-2)

3-Benzoylindole,
Methanone, 1H-indole-3-ylphenyl- (15224-25-6)

1,3-propanedithiol (109-80-8)

2-Phenyl-1,3-dithiane (5425-44-5)

2-methylthio-2-phenyl-1,3-dithiane (34858-82-7)

3-Benzylindole,
1H-Indole, 3-(phenylmethyl) (16886-10-5)

1,10-phenanthroline (66-71-7)

1,3-dithian-2-yl carbenium

2-methoxy-1,3-dithiane

2-methoxy-1,3-dithiolane

1,3-Dithiane,
1,3-dithian (505-23-7)

1,3-dithian-2-yltrimethylammonium iodide

1,3-dithian-2-yl fluoroborate

trityl fluoroborate

2-chloro-1,3-dithiane

3-(2-phenyl-1,3-dithian-2-yl)-1H-indole (57621-00-8)