



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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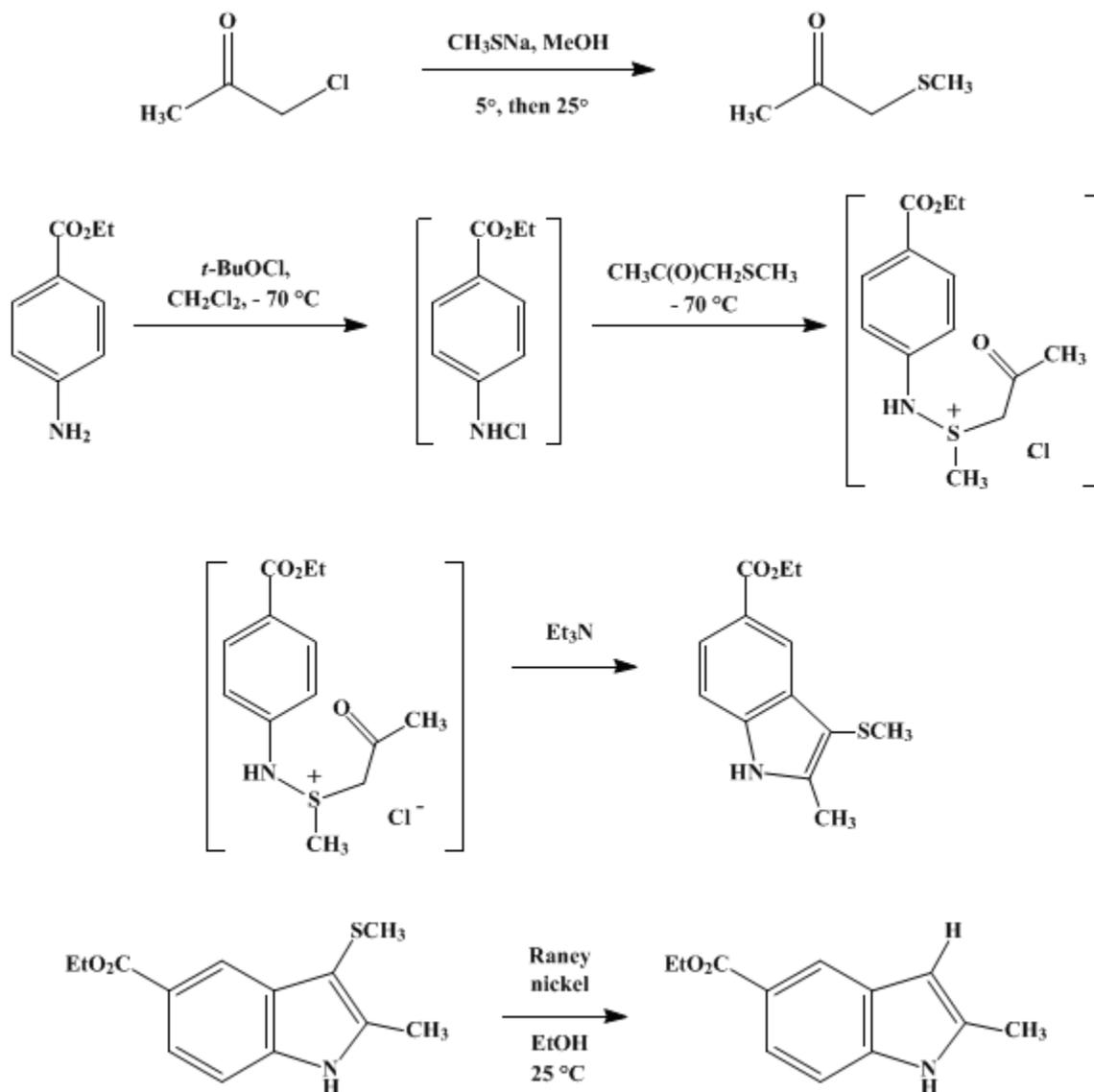
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 6, p.601 (1988); Vol. 56, p.72 (1977).*

## INDOLES FROM ANILINES: ETHYL 2-METHYLINDOLE-5-CARBOXYLATE

[1*H*-Indole-5-carboxylic acid, 2-methyl, ethyl ester]



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### 1. Procedure

*Caution! Part A must be conducted in an efficient hood to avoid exposure to methanethiol and chloroacetone, both of which are highly irritating. In Part C, the usual precautions associated with the pyrophoric reagent Raney nickel (Note 12) should be observed.*

A. *Methylthio-2-propanone*.<sup>2</sup> A 2-l., three-necked, round-bottomed flask is equipped with a sealed mechanical stirrer and a two-necked adapter holding a thermometer and a condenser topped with a silica

gel drying tube. After 700 ml. of anhydrous **methanol** has been added, the third neck is stoppered, and the flask is immersed in an ice water bath. Stirring is begun, and 108 g. (2.00 moles) of **sodium methoxide** (Note 1) is added in small portions at a rate sufficiently gradual to prevent a large exotherm (Note 2). When all of the **methoxide** has dissolved and the temperature has returned to 5°, the stopper is replaced with a 200-ml., pressure-equalizing, jacketed addition funnel (Note 3). This funnel, charged previously with 130 ml. (2.20 moles) of **methanethiol** (Note 4), contains a 2-propanol-dry ice slurry in the cooling jacket, and is topped with a silica gel drying tube. Stirring and cooling are continued while the **methanethiol** is run into the flask over a 20-minute period, and for 15 minutes thereafter. The jacketed addition funnel is then replaced by a standard, 200-ml., pressure-equalizing addition funnel, which is used to add 185 g. (2.00 moles) of **chloroacetone** (Note 5) to the reaction mixture over 1 hour. When this addition is complete, the ice bath is removed, and the suspension is stirred overnight at room temperature. The insoluble material, largely inorganic salts, is removed by filtration through Celite, and the filter cake is washed with two 150-ml. portions of absolute **methanol**. After **methanol** has been removed from the combined filtrates by distillation, the residue is distilled through a 300-mm. Vigreux column, yielding 155–158 g. (74–76%) of **methylthio-2-propanone**, b.p. 153–154°,  $n_D^{23}$  1.4728.

B. *Ethyl 2-methyl-3-methylthioindole-5-carboxylate*. A 1-l., three-necked, round-bottomed flask is equipped with a sealed mechanical stirrer, a 100-ml., pressure-equalizing addition funnel, and a two-necked adapter holding a low-temperature thermometer and a gas-inlet tube. The flask is charged with 16.5 g. (0.100 mole) of **ethyl 4-aminobenzoate** (Benzocaine) (Note 6) and 500 ml. of **dichloromethane** (Note 7), and a positive pressure of dry **nitrogen** is established while the solution is stirred and cooled to –70° with a 2-propanol–dry-ice bath. The resulting suspension is stirred vigorously, and a solution of 10.8 g. (0.0995 mole) of *tert*-butyl hypochlorite [*Org. Synth.*, Coll. Vol. 5, 184 (1973)] in 50 ml. of **dichloromethane** (Note 7) is added dropwise over a 10-minute period. The reaction mixture is stirred for 1 hour at –70°, followed by dropwise addition of a solution of 10.4 g. (0.100 mole) of **methylthio-2-propanone** in 50 ml. of **dichloromethane** (Note 7) over 10 minutes. A slight exotherm (*ca.* 5°) is noted during the addition, resulting in a clear yellow solution. After stirring for another hour at –70°, during which time a suspension of precipitated salts forms, a solution of 10.1 g. (0.100 mole) of **triethylamine** (Note 8) in 30 ml. of **dichloromethane** (Note 7) is added dropwise over 10 minutes. After an additional 15 minutes at –70°, the cooling bath is removed.

When the reaction mixture has warmed to room temperature, stirring is made more vigorous, and 100 ml. of water is added. The layers are separated, and the organic phase is dried over anhydrous **magnesium sulfate** and filtered. Removal of **dichloromethane** with a rotary evaporator leaves an oily residue, which is cooled in an ice bath, inducing crystallization. The resulting solid is stirred with 50 ml. of **diethyl ether** for 30 minutes at 0° (Note 9), collected by filtration, and washed with 25 ml. of **ether** at 0°. Concentration of the filtrate to 15 ml. and chilling at *ca.* 5° overnight yields a second crop of crystalline product, bringing the total crude yield to 14.7–18.0 g. (59–73%), m.p. 120.5–124° (Note 10). Recrystallization from absolute **ethanol** (5 ml. per 2 g.) yields 12.8–17.5 g. (51–70%) of **ethyl 2-methyl-3-methylthioindole-5-carboxylate**, m.p. 125.5–127°.

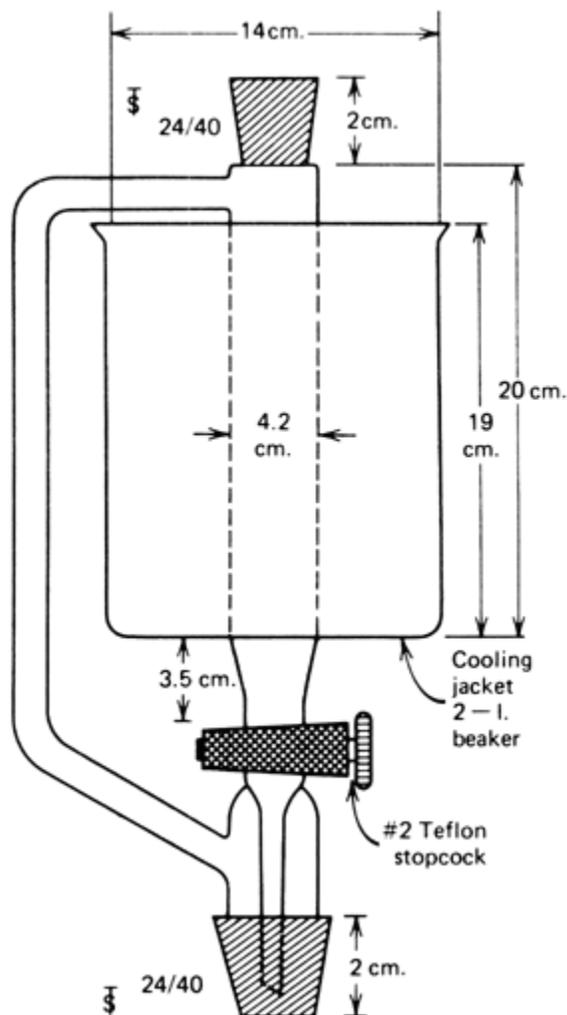
C. *Ethyl 2-methylindole-5-carboxylate*. A solution of 10.0 g. (0.0402 mole) of **ethyl 2-methyl-3-methylthioindole-5-carboxylate** in 300 ml. of absolute **ethanol** is placed in a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer. An excess (15 teaspoons), (Note 11) of freshly washed W-2 Raney nickel (Note 12) is added, and the mixture is stirred for one hour. Stirring is then stopped, the liquid phase is decanted, and the catalyst is washed twice by stirring for 15 minutes with 100-ml. portions of absolute **ethanol** and decanting the solvent. The combined ethanolic solutions are concentrated on a rotary evaporator. The residual solid is dissolved in 150 ml. of warm **dichloromethane**, dried over anhydrous **magnesium sulfate**, and filtered; the drying agent is washed with 40 ml. of **dichloromethane**. Concentration of the combined filtrates with a rotary evaporator gives 7.5–8.1 g. (93–99%) of **ethyl 2-methylindole-5-carboxylate**, m.p. 140.5–142.0° (Note 13).

## 2. Notes

1. **Sodium methoxide** was purchased from MC and B Manufacturing Chemists and used without further purification. Accurate weighing is important, since the checkers noted that an excess of **methoxide** relative to **chloroacetone**, however slight, led to little or no product.

- A convenient technique is to add the methoxide from an Erlenmeyer flask, connected to the previously stoppered neck of the reaction flask by a piece of flexible rubber tubing (Gooch tubing).
- The addition funnel used in this preparation is depicted in Figure 1.

Figure 1.



- Methanethiol** was purchased from Matheson Gas Products. *Caution! This compound has a powerful, vile odor, even at extremely low concentrations.* The gas, which liquefies at 6°, may be condensed by calibrating the addition funnel at 130 ml. with a grease pencil, inserting a cold-finger condenser topped with a gas-inlet tube in the female joint, and protecting the male joint from moisture by a drying tube. A 2-propanol–dry-ice slurry is placed in the condenser and the cooling jacket, and **methanethiol** is introduced through the gas-inlet until the condensed liquid reaches the calibration mark.
- Chloroacetone** was purchased from Distillation Products (Eastman Organic Chemicals) and distilled prior to use. *Caution! This compound is an intensely powerful lachrymator.*
- Ethyl p-aminobenzoate** was purchased from the Aldrich Chemical Company, Inc., and used without further purification.
- Commercial **dichloromethane** was distilled prior to use.
- Triethylamine** was purchased from the J. T. Baker Chemical Company and used without further purification.
- If the **ether** is added prior to crystallization, a slightly reduced yield results.
- Occasionally the product is contaminated with an impurity (1–2%), which appears as tiny red needles. This material has been tentatively identified as **diethyl azobenzene-4,4'-dicarboxylate**.
- A level teaspoonful contains about 3 g. of **nickel**.
- W-2 Raney nickel was purchased from W. R. Grace and Co. Prior to use it was washed with distilled water until neutral, then three times with absolute ethanol [*Org. Synth.*, **Coll. Vol. 3**, 181

(1955)]. This material may ignite spontaneously if allowed to become dry. Thus, in decanting, a small amount of solvent must be left behind to cover the catalyst. Although environmentally unsound, spent catalyst is discarded by slurring in water and flushing the slurry down the drain with running water.

13. Little change in melting point results when the product is recrystallized from [benzene](#).

### 3. Discussion

This procedure is an example of a new [indole](#) synthesis, which can be utilized to prepare 1-, 2-, 4-, 5-, 6-, or 7-substituted indoles.<sup>3</sup> Indoles substituted on the phenyl ring with nitro, ethoxycarbonyl, chloro, methyl, and acetoxy groups have been prepared; hydrogen, methyl, and phenyl groups have been placed in the 2-position; and the method has been used to prepare 1-methylindoles. A similar procedure substituting  $\alpha$ -thioesters for  $\alpha$ -thioketones yields oxindoles in good overall yields.<sup>4</sup> The major advantages of this sequence are the availability of starting materials and the high overall yields of indoles and oxindoles realized.<sup>5</sup>

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### References and Notes

1. Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. [Present address: Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455.]
2. C. K. Bradsher, F. C. Brown, and R. J. Grantham, *J. Am. Chem. Soc.*, **76**, 114 (1954).
3. P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **95**, 590 (1973); P. G. Gassman, T. J. van Bergen, and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **95**, 5608 (1973); P. G. Gassman, D. P. Gilbert, and T. J. van Bergen, *J. Chem. Soc. Chem. Commun.*, 201 (1974); P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Am. Chem. Soc.*, **96**, 5495 (1974); P. G. Gassman, G. D. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5512 (1974); P. G. Gassman, D. P. Gilbert, and T.-Y. Luh, *J. Org. Chem.*, **42**, 1340 (1977).
4. P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **95**, 2718 (1973); P. G. Gassman, T. J. van Bergen, and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **95**, 5608 (1973); P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5508 (1974); P. G. Gassman, G. D. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5512 (1974); P. G. Gassman, D. P. Gilbert, and T.-Y. Luh, *J. Org. Chem.*, **42**, 1340 (1977); P. G. Gassman, B. W. Cue, Jr., and T.-Y. Luh, *J. Org. Chem.*, **42**, 1344 (1977); P. G. Gassman and R. L. Parton, *J. Chem. Soc. Chem. Commun.*, 694 (1977); P. G. Gassman and K. M. Halweg, *J. Org. Chem.*, **44**, 628 (1979).
5. For a summary of other [indole](#) syntheses, see R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970.

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### Appendix

#### Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

W-2 Raney nickel

[ethanol](#) (64-17-5)

[Benzene](#) (71-43-2)

[methanol](#) (67-56-1)

[ether](#),  
[diethyl ether](#) (60-29-7)

nitrogen (7727-37-9)

nickel,  
Raney nickel (7440-02-0)

sodium methoxide (124-41-4)

dichloromethane (75-09-2)

methoxide

chloroacetone (78-95-5)

magnesium sulfate (7487-88-9)

methanethiol (74-93-1)

Indole (120-72-9)

triethylamine (121-44-8)

ethyl 4-aminobenzoate,  
Ethyl p-aminobenzoate (94-09-7)

Ethyl 2-methylindole-5-carboxylate,  
1H-Indole-5-carboxylic acid, 2-methyl, ethyl ester (53600-12-7)

methylthio-2-propanone (14109-72-9)

Ethyl 2-methyl-3-methylthioindole-5-carboxylate

tert-Butyl hypochlorite (507-40-4)

diethyl azobenzene-4,4'-dicarboxylate