Organic
Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

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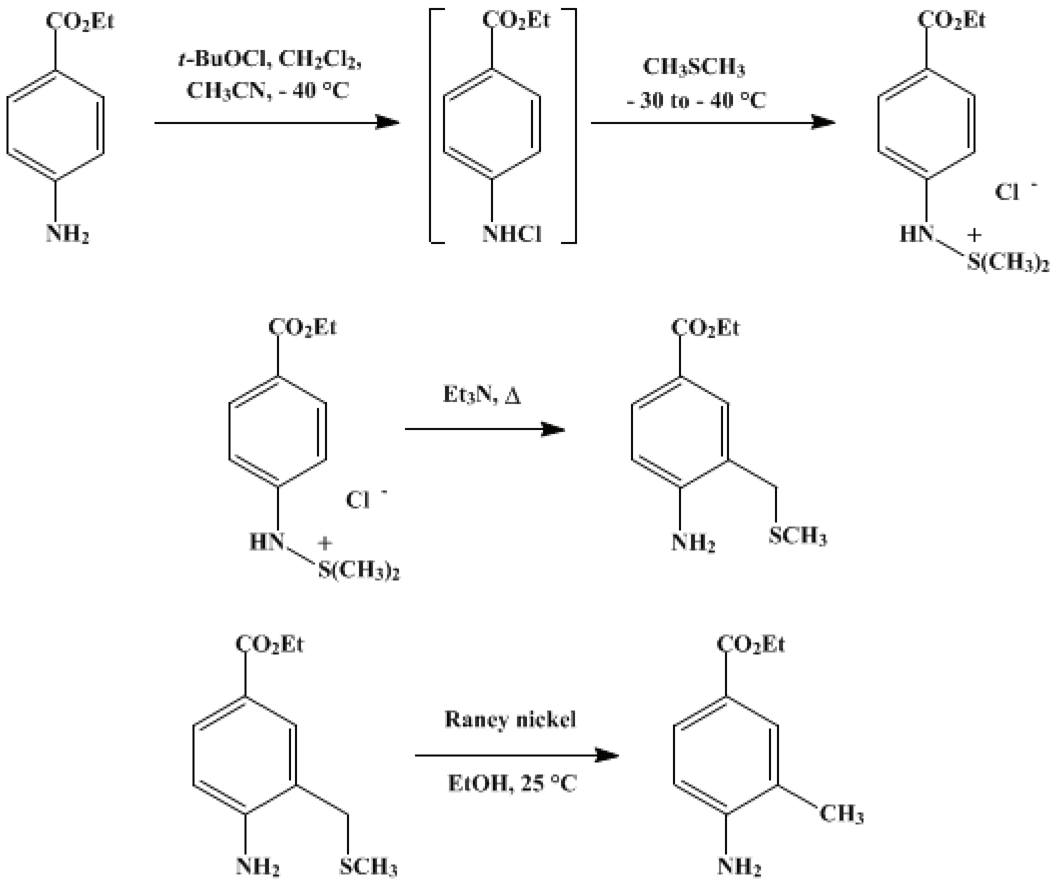
ortho-ALKYLATION OF ANILINES: ETHYL 4-AMINO-3-METHYLBENZOATE

[Benzoic acid, 4-amino-3-methyl-, ethyl ester]



Submitted by P. G. Gassman[12] and G. Gruetzmacher.
Checked by M. Savitsky, R. R. Schmidt, III, and G. Büchi.

1. Procedure

Caution! Part A must be conducted in a hood due to the noxious odor of dimethyl sulfide. In Part B, the usual precautions associated with the pyrophoric reagent Raney nickel must be observed (see (Note 8)).

A. *Ethyl 4-amino-3-(methylthiomethyl)benzoate.* A 1-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a condenser topped with a gas-inlet tube, a two-necked adapter holding a low-temperature thermometer, and a 100-ml., pressure-equalizing dropping funnel. The flask is charged with 16.50 g. (0.1000 mole) of ethyl 4-aminobenzoate (Benzocaine, (Note 1)), 300 ml. of acetonitrile, and 100 ml. of dichloromethane, flushed with nitrogen, and immersed in a 40% aqueous methanol–dry-ice bath maintained between −40° and −50° (Note 2). When the reaction mixture has come to −40°, a solution of 10.85 g. (0.1000 mole) of *tert*-butyl hypochlorite [*Org. Synth.*, **Coll. Vol. 5**, 184 (1973)] in 25 ml. of dichloromethane is added dropwise over a 15-minute period. The addition funnel is rinsed with 25 ml. of dichloromethane, the reaction solution is stirred for another 5 minutes, and 23 g. (25 ml., 0.34 mole) of dimethyl sulfide (Note 3) is added at a rate that allows the vigorously stirred reaction mixture to be maintained below −30°.

Shortly after the addition is complete, a voluminous white precipitate appears, and the resulting slurry is stirred and maintained at −50° to −40° for 4 hours. Cooling and stirring are continued as 18 g. (25 ml., 0.18 mole) of triethylamine (Note 4) is added dropwise, during which time the reaction mixture first goes to a clear solution, then becomes cloudy. The resulting mixture is stirred at −50° to −40° for 1 hour.

The cooling bath is then replaced with a steam bath, and the reaction mixture is refluxed for 16 hours. It is then cooled, transferred to a one-necked, 1-l., round-bottomed flask, and concentrated to dryness on a rotary evaporator. The dark residue is dissolved in a mixture of 200 ml. of water, 200 ml. of dichloromethane, and 20 ml. of triethylamine, and the aqueous phase is separated and washed with two 200-ml. portions of dichloromethane. The organic phases are combined and washed with 300 ml. of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent on a rotary evaporator gives a red oil, which solidifies on storage at 0–5° (Note 5). Recrystallization of this solid from 40 ml. of absolute ethanol gives 7.6–8.4 g. (34–37%) of ethyl 4-amino-3-(methylthiomethyl)benzoate, m.p. 83–85°. A second crop of 1.1–2.5 g. of crystalline material, m.p. 78–83°, may be obtained by concentration of the mother liquors (Note 6).

B. *Ethyl* 4-*Amino*-3-*methylbenzoate.* A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser, and a nitrogen-inlet tube is charged with 11.25 g. (0.05000 mole) of ethyl 4-amino-3-(methylthiomethyl)benzoate, 300 ml. of absolute ethanol, and 17 teaspoons (*ca.* 50 g.) of W-2 Raney nickel (Note 7). The reaction mixture is stirred at 25° for one hour before stirring is discontinued, and the ethanolic solution is decanted from the catalyst (Note 8). The catalyst is then washed with one 300-ml. portion of absolute ethanol and one 500-ml. portion of dichloromethane, the solvent being removed by decanting in each case. The organic solutions are combined and concentrated on a rotary evaporator, giving a solid which is dissolved in 200 ml. of dichloromethane, dried over anhydrous magnesium sulfate, filtered, and taken to dryness on a rotary evaporator, yielding 7.0–7.6 g. (77–84%) of ethyl 4-amino-3-methylbenzoate as a white solid, m.p. 75–78°.

2. Notes

1. Benzocaine was purchased from Mallinckrodt Chemical Works and recrystallized from absolute ethanol prior to use to give material of m.p. 91–92°.
2. Fairly precise temperature control is required, since the reaction mixture begins to solidify at about −50°.
3. Dimethyl sulfide was purchased from MC and B Manufacturing Chemists and used without further purification.
4. Triethylamine was purchased from the J. T. Baker Chemical Company and used without further purification.
5. Solidification is facilitated by dissolving the oil in a minimum amount of diethyl ether (*ca.* 100 ml.) and removing the ether on a rotary evaporator. Should the oil still refuse to solidify, this process is repeated several times with pentane.
6. The second crop of crystalline material is contaminated with a small amount of ethyl *p*-aminobenzoate and usually red-orange in color. It is of sufficient purity to be used in Part B.
7. W-2 Raney nickel was purchased from W. R. Grace & Company. Prior to use it was washed with distilled water until the washings were neutral, then washed three times with absolute ethanol and stored under ethanol until needed [*Org. Synth.*, **Coll. Vol. 3**, 181 (1955)].
8. Activated Raney nickel is pyrophoric and should never be allowed to become dry. Thus, decanting is preferred to filtration, and when decanting, a small amount of solvent must always be left behind to cover the catalyst powder. For safe (but environmentally unsound) disposal, the spent catalyst should be slurried in water and flushed down the drain under running water.

3. Discussion

This procedure illustrates a general method for the *ortho*-alkylation of anilines.[3] It can be utilized for both anilines and mono-*N*-substituted anilines, with a variety of functional groups on the aromatic ring. By substituting α-thioketones and α-thioesters for dialkyl sulfides, the method has been extended to produce indoles[4] and oxindoles,[5] respectively. An example of the indole synthesis appears elsewhere in this volume. Ethyl 4-amino-3-methylbenzoate has been reported previously.[6]

References and Notes

1. Department of Chemistry, The Ohio State University, Columbus, Ohio 43210.
2. Present address: Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455.
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4. P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **95**, 590 (1973).
5. P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **95**, 2718 (1973).
6. F. J. Viliani, U.S. Patent 2,764,519 (1956) [*Chem. Abstr.*, **51**, 4443*e* (1957)].

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

ethanol (64-17-5)

ether,
diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

dimethyl sulfide (75-18-3)

Indole (120-72-9)

triethylamine (121-44-8)

Ethyl 4-amino-3-methylbenzoate,
Benzoic acid, 4-amino-3-methyl-, ethyl ester (40800-65-5)

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

Ethyl 4-amino-3-(methylthiomethyl)benzoate (50461-34-2)

tert-Butyl hypochlorite (507-40-4)