Organic Syntheses

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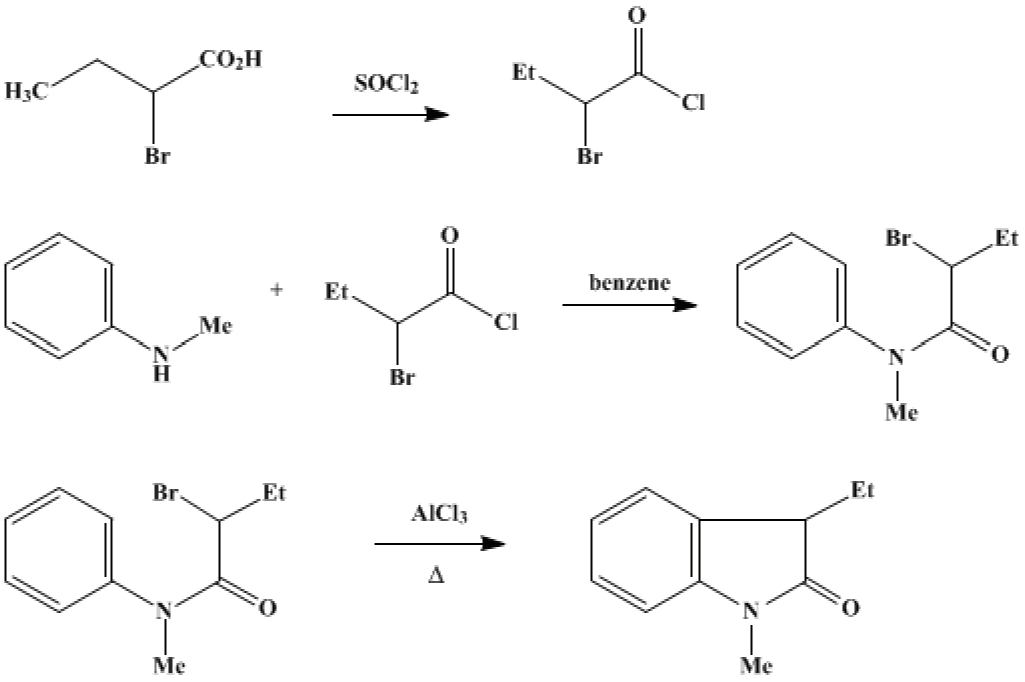
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.030.0062

Organic Syntheses, Coll. Vol. 4, p.620 (1963); Vol. 30, p.62 (1950).

1-METHYL-3-ETHYLOXINDOLE

[Oxindole, 3-ethyl-1-methyl]



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1. Procedure

In a 500-ml. round-bottomed flask fitted with a calcium chloride drying tube are placed 226 g. (1.35 moles) of α-bromo-*n*-butyric acid (Note 1) and 284 g. (175 ml., 2.39 moles) of thionyl chloride (Note 2). A small piece of porous plate is added, and the reaction mixture is allowed to stand at room temperature for 48 hours (Note 3). The excess thionyl chloride is removed by distillation, and the acid chloride is collected at 147–153° (Note 4). The yield of colorless product is 168–197 g. (67–78%).

In a 1-l. three-necked flask fitted with a Hershberg wire stirrer, a reflux condenser equipped with a calcium chloride drying tube, and a dropping funnel, are placed 237 g. (2.21 moles) of methylaniline (Note 5) and 300 ml. of dry benzene (Note 6). Stirring is started, and the reaction mixture is cooled in an ice-water bath during the dropwise addition of 197 g. (1.06 moles) of α-bromo-*n*-butyryl chloride diluted with approximately 40 ml. of dry benzene. The addition requires approximately 1 hour, and the reaction mixture becomes thick owing to the separation of methylaniline hydrochloride. The mixture is stirred for an additional 30 minutes and is then set aside protected by a calcium chloride tube for approximately 12 hours. The colorless methylaniline hydrochloride is removed by filtration with suction and washed with two 25-ml. portions of benzene. The combined filtrate and washings are washed with three 100-ml. portions of 5% hydrochloric acid to remove excess methylaniline, and then with two 100-ml. portions of water (Note 7). The benzene layer is dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the solvent is removed by distillation (the last traces of solvent are removed with an aspirator) to give N-methyl-α-bromo-*n*-butyranilide (Note 8).

The crude N-methyl-α-bromo-*n*-butyranilide is placed in a 500 ml. three-necked round-bottomed flask equipped with a Hershberg wire stirrer and a reflux condenser fitted with a calcium chloride drying tube. To the stirred liquid, cooled in an ice-water bath, is added 281 g. (2.1 moles) of aluminum chloride (reagent grade, powdered) in portions over a period of about 30 minutes (Note 9). A thermometer is then introduced, and the cooling bath is replaced by a source of heat (Note 10). The reaction commences at about 80° with the evolution of hydrogen bromide (Note 11) and becomes very vigorous at 95–105°. At this point, no external heat need be applied, because the heat of reaction carries the temperature to 110–115°. When the reaction slows down, the temperature is raised to 160–170°, and the dark mixture is then allowed to cool to about 80–90°. The reaction mixture is poured *cautiously* into a 3-l. beaker about one-fourth full of cracked ice. Additional ice is added as required. The last traces of product are removed from the flask with the aid of hydrochloric acid and ice. Concentrated hydrochloric acid (75 ml.) is added to aid the decomposition of the aluminum chloride complex. The brown oil is separated after adding 75 ml. of ether, and the aqueous layer is extracted with two 100-ml. portions of ether. The combined organic layers are washed with two 75-ml. portions of 5% hydrochloric acid, two 100-ml, portions of water, two 75-ml. portions of saturated sodium bicarbonate solution, and two 100-ml. portions of water. After drying over anhydrous magnesium sulfate the ether is distilled, and the residue is distilled under reduced pressure. The main fraction is collected at 103–107°/0.5 mm. The yield is 126–131 g. (68–71% based on the acid chloride) of pale yellow 1-methyl-3-ethloxindole, n_{D}^{25} 1.5569–1.5580.

2. Notes

1. The α-bromo-*n*-butyric acid obtained from the Eastman Kodak Company, which had a boiling range of 2°, proved to be satisfactory.
2. Commercial thionyl chloride was distilled before use.
3. The reaction mixture is allowed to stand under an efficient hood during this period. A yield of 166 g. of product may be obtained by refluxing the mixture for 2.5 hours in a 1-l. flask equipped with condenser and drying tube.
4. The submitters used apparatus fitted with ground-glass joints for this and subsequent operations.
5. Redistilled N-methylaniline was used, b.p. 195–196°.
6. The benzene was dried by distillation.
7. Sodium chloride was added to the hydrochloric acid solution and to the wash water to reduce emulsion formation.
8. The crude N-methyl-α-bromo-*n*-butyranilide may be used directly for the ring closure or, if desired, may be purified by distillation (b.p. 117–118°/0.4 mm., 125–127°/0.8 mm., 175–184°/24 mm.).
9. The aluminum chloride is introduced into the reaction mixture without exposure to the atmosphere.[2] The mixture becomes quite viscous, and a powerful stirrer is needed.
10. An electric heating jacket was found to be most satisfactory.
11. The reaction should be carried out under an efficient hood with provision for the absorption of evolved hydrogen bromide.

3. Discussion

This method is a general one for the preparation of oxindoles and 1-methyoxindoles, and is based on the procedure of Stollé[3] as developed by Julian and Pikl.[4]

1-Methyl-3-ethyloxindole has been prepared previously by methylation of 3-ethyloxindole with methyl iodide.[5] It has also been made from 1-methyloxindole by acylation with ethyl acetate in the presence of sodium ethoxide, followed by hydrogenation over a palladium catalyst.[6]

References and Notes

1. University of Pennsylvania, Philadelphia 4, Pennsylvania.
2. Fieser, *Experiments in Organic Chemistry*, 3rd ed., p. 265, D. C. Heath and Company, Boston, 1955.
3. Stollé, *J. prakt. Chem.*, [2] **128**, 1 (1930).
4. Julian and Pikl, *J. Am. Chem. Soc.*, **57**, 563 (1935). Porter, Robinson, and Wyler, *J. Chem. Soc.*, **1941**, 620.
5. Brunner, *Monatsh.*, **18**, 545 (1897).
6. Julian, Pikl, and Wantz, *J. Am. Chem. Soc.*, **57**, 2026 (1935).

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

1-methyl-3-ethloxindole

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

hydrogen bromide (10035-10-6)

aluminum chloride (3495-54-3)

sodium ethoxide (141-52-6)

palladium (7440-05-3)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

methylaniline,
N-Methylaniline (100-61-8)

1-Methyl-3-ethyloxindole,
Oxindole, 3-ethyl-1-methyl (2525-35-1)

methylaniline hydrochloride (2739-12-0)

3-ethyloxindole

1-methyloxindole (61-70-1)

α-bromo-n-butyric acid (80-58-0)

α-bromo-n-butyryl chloride (22118-12-3)

N-methyl-α-bromo-n-butyranilide