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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 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.

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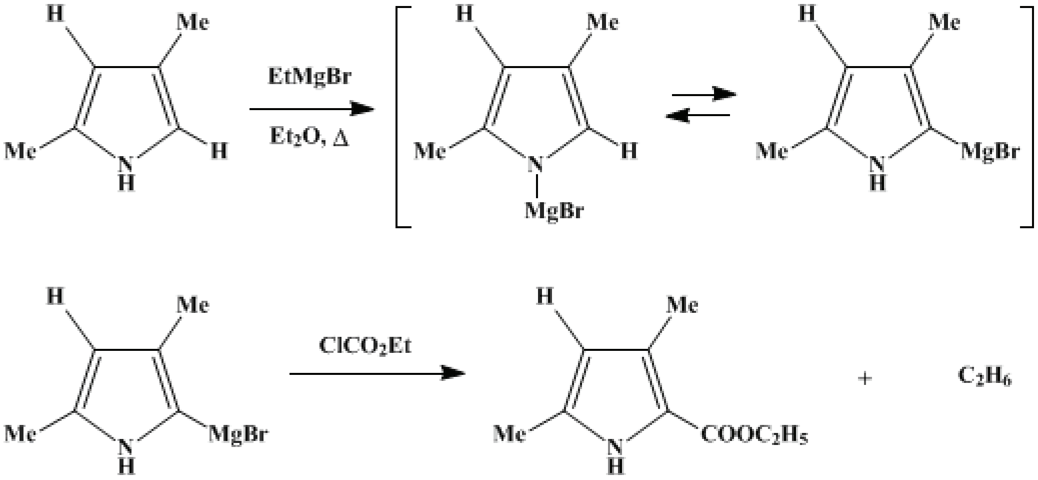
2,4-DIMETHYL-5-CARBETHOXYPYRROLE

[2-Pyrrolecarboxylic acid, 3, 5-dimethyl-, ethyl ester]



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1. Procedure

In a 1-l. round-bottomed, three-necked flask fitted with an efficient reflux condenser, liquid-sealed stirrer, and dropping funnel is placed 13 g. (0.53 gram atom) of magnesium turnings. A few cubic centimeters of a solution of 60 g. (42 cc., 0.55 mole) of pure ethyl bromide in 50 cc. of absolute ether is added and the stirrer started (Note 1). When the bromide begins to react 200 cc. of absolute ether is added, and then the balance of the bromide solution is run in as fast as the refluxing permits (about one-half hour). After allowing fifteen minutes for the completion of the reaction, a solution of 40 g. (0.42 mole) of 2,4-dimethylpyrrole (p. 217) in 100 cc. of absolute ether is added in the course of twenty minutes (Note 2) and the mixture is refluxed for one-half hour on the steam bath.

The reaction mixture is cooled to room temperature, and a solution of 58 g. (51 cc., 0.53 mole) of freshly distilled ethyl chloroformate (b.p. 92.5–93.5°) in 100 cc. of absolute ether is added dropwise in the course of one-half hour (Note 3). The mixture is heated on the steam bath for one and one-half hours and then allowed to stand overnight at room temperature.

The flask is placed in an ice-salt mixture, and the contents are decomposed by the gradual addition of 300 cc. of saturated ammonium chloride solution and 100 cc. of water (Note 4). The aqueous layer is removed by means of a 1.5-l. separatory funnel, and sufficient ether is added to dissolve the yellow precipitate. The total volume of ether solution is about 1 l. This is washed with two 200-cc. portions of water, and the three aqueous layers are extracted consecutively with a 100-cc. portion of ether. The combined ether solution is dried over 30 g. of anhydrous sodium sulfate, concentrated on the steam bath to a volume of about 200 cc., and cooled to room temperature. The product which crystallizes is collected with suction and washed with two 25-cc. portions of ether. The yield is 35–38 g. of light yellow product, m.p. 122–123°. The ether is completely removed from the combined filtrates by heating on the steam bath, and the black oil is allowed to stand overnight. The semi-solid mass is filtered with suction and washed with a minimum amount of cold ether. In this way an additional 6–7 g. of yellow material is obtained which melts at 119–121°.

The combined crude material is crystallized from 75 cc. of 95 per cent alcohol and yields 37–39 g. of slightly colored material, m.p. 123–124°. A second crystallization from alcohol gives 34–36 g. of colorless product melting at the same temperature. By the systematic working of the alcoholic mother liquors, an additional 5–6 g. of pure material is obtained, making the total yield 40–41 g. (57–58 per cent of the theoretical amount).

2. Notes

1. Stirring is continued without interruption throughout the preparation to the point where the mixture is allowed to stand overnight.
2. The reaction is not exothermic, but the large volume of ethane evolved necessitates the regulated addition of the solution of dimethylpyrrole.
3. Considerable heat is produced during the addition of about two-thirds of the solution, after which the addition may be more rapid.
4. The first third of the ammonium chloride solution must be added quite slowly with frequent and thorough shaking.

3. Discussion

The most convenient laboratory method for the preparation of 2,4-dimethyl-5-carbethoxypyrrole is that given above.[1] A cheaper method of obtaining large quantities of the material consists in the partial hydrolysis of 2,4-dimethyl-3,5-dicarbethoxypyrrole with sulfuric acid, followed by decarboxylation.[2] The ester has been obtained also by the alcoholysis of 5-trichloroaceto-2,4-dimethylpyrrole in the presence of sodium ethoxide.[3] The free acid has been obtained from 1-[2,4-dimethylpyrrole-5]-2,4-dimethylpyrrole-5-carboxylic acid[4] and from 2,4-dimethylpyrrole-5-aldehyde.[5]

References and Notes

1. Fischer, Weiss, and Schubert, Ber. **56**, 1199 (1923); Ingraffia, Gazz. chim. ital **63**, 584 (1933).
2. Fischer and Walach, Ber. **58**, 2820 (1925).
3. Houben and Fischer, ibid. **64**, 2639 (1931).
4. Magnanini, ibid. **22**, 38 (1889).
5. Alessandri, Atti accad. Lincei **24** (II) 199 (1915) [C. A. **10**, 1350 (1916)]; Alessandri and Passerini, Gazz. chim. ital. **51** (I), 277 (1921).

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

1-[2,4-dimethylpyrrole-5]-2,4-dimethylpyrrole-5-carboxylic acid

alcohol (64-17-5)

sulfuric acid (7664-93-9)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

sodium ethoxide (141-52-6)

ethyl chloroformate (541-41-3)

2,4-Dimethyl-5-carbethoxypyrrole,
2-Pyrrolecarboxylic acid, 3, 5-dimethyl-, ethyl ester (2199-44-2)

2,4-Dimethylpyrrole (625-82-1)

ethane (74-84-0)

dimethylpyrrole

2,4-Dimethyl-3,5-dicarbethoxypyrrole (2436-79-5)

5-trichloroaceto-2,4-dimethylpyrrole

2,4-dimethylpyrrole-5-aldehyde