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.

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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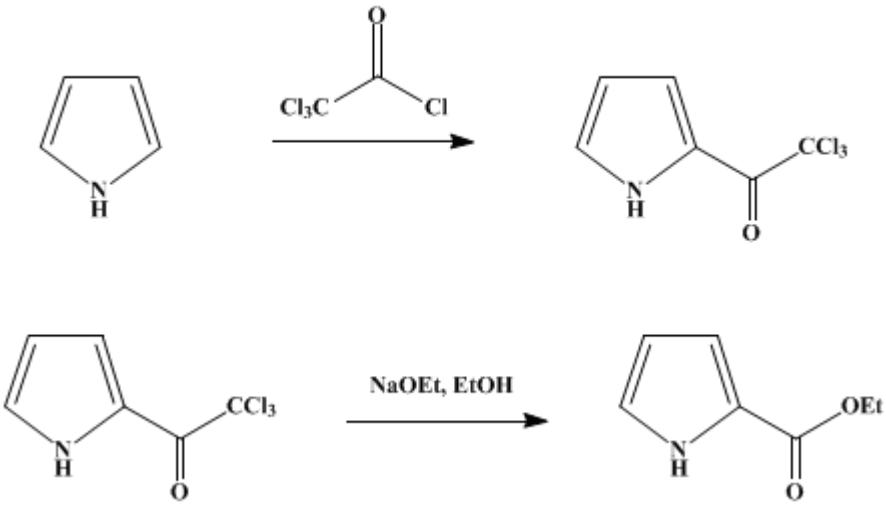
ETHYL PYRROLE-2-CARBOXYLATE

[1*H*-Pyrrole-2-carboxylic acid, ethyl ester]



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Checked by A. Brossi and P. Wehrli.

1. Procedure

A. *2-Pyrrolyl trichloromethyl ketone*. A 3-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a dropping funnel, and an efficient reflux condenser with a calcium chloride drying tube is charged with 225 g. (1.23 moles) of trichloroacetyl chloride and 200 ml. of anhydrous diethyl ether. The solution is stirred while 77 g. (1.2 moles) of freshly distilled pyrrole in 640 ml. of anhydrous ether is added over 3 hours (Note 1); the heat of reaction causes the mixture to reflux. Following the addition, the mixture is stirred for 1 hour before 100 g. (0.724 mole) of potassium carbonate in 300 ml. of water is slowly added through the dropping funnel (Note 2). The layers are separated, and the organic phase is dried with magnesium sulfate, treated with 6 g. of Norit, and filtered. The solvent is removed by distillation on a steam bath, and the residue is dissolved in 225 ml. of hexane. The dark solution is cooled on ice to induce crystallation. The tan solid is collected and washed with 100 ml. of cold hexane, giving 189–196 g. (77–80%) of the ketone, m.p. 73–75° (Note 3).

B. *Ethyl pyrrole-2-carboxylate*. A 1-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer and powder funnel is charged with 1.0 g. (0. 44 g.-atom) of sodium and 300 ml. of anhydrous ethanol. When the sodium is dissolved, 75 g. (0.35 mole) of 2-pyrrolyl trichloromethyl ketone is added portionwise over a 10-minute period (Note 4). Once the addition is complete, the solution is stirred for 30 minutes, then concentrated to dryness using a rotary evaporator. The oily residue is partitioned between 200 ml. of ether and 25 ml. of 3 *N* hydrochloric acid. The ether layer is separated, and the aqueous layer is washed once with 100 ml. of ether. The combined ether solutions are washed once with 25 ml. of saturated sodium hydrogen carbonate solution, dried with magnesium sulfate, and concentrated by distillation. The residue is fractionated at reduced pressure, giving 44.0–44.5 g. (91–92%) of ethyl pyrrole-2-carboxylate as a pale yellow oil, b.p. 125–128° (25 mm.) (Note 5). The yield based on pyrrole is 70–74%. Upon standing at room temperature the product crystallizes, m.p. 40–42°.

2. Notes

1. If the addition time is shortened to 1 hour, the yield is decreased by about 5%.
2. Excessive frothing will occur if the potassium carbonate solution is added too fast.

3. A similar run on a scale 3.3 times as large with a 3-hour addition time gave the ketone in 74% yield.
4. The solution becomes warm during the addition, and the final color of the solution is reddish-brown.
5. A similar run on a scale three times as large gave the ester in 96% yield.

3. Discussion

Pyrrole-2-carboxylic acid esters have been prepared from ethyl chloroformate and pyrrolylmagnesium bromide[2] or pyrrolyllithium,[3] by hydrolysis and decarboxylation of dimethyl pyrrole-1,2-dicarboxylate followed by re-esterification of the 2-acid[4] and by oxidation of pyrrole-2-carboxaldehyde followed by esterification with diazomethane.[4]

Methods of acylating pyrrole similar to the present, using oxalyl chloride,[5] trifluoroacetic anhydride,[6] carbamic acid chloride,[7] and trichloroacetyl chloride,[8] have been reported. In the last preparation, it was necessary to separate the product from highly colored by-products with alumina chromatography. 2-Pyrrolyl trichloromethyl ketone has also been prepared by the reaction of pyrrolylmagnesium halide with trichloroacetyl chloride.[9]

The present procedure provides a facile and versatile synthesis, on large scale, of a variety of pyrrole-2-carboxylic acid derivatives without necessitating the use of moisture-sensitive organometallic reagents. The use of alcohols other than ethanol in the alcoholysis reaction provides virtually any desired ester. Ammonia or aliphatic amines readily give amides in high yields, and aqueous base can be used to give the free acid.

References and Notes

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

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether,
diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

sodium (13966-32-0)

ethyl chloroformate (541-41-3)

Pyrrole (109-97-7)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

carbamic acid chloride

oxalyl chloride (79-37-8)

hexane (110-54-3)

Pyrrole-2-carboxaldehyde (1003-29-8)

trifluoroacetic anhydride (407-25-0)

trichloroacetyl chloride (76-02-8)

Ethyl pyrrole-2-carboxylate,
1H-Pyrrole-2-carboxylic acid, ethyl ester (2199-43-1)

2-pyrrolyl trichloromethyl ketone (35302-72-8)

Pyrrole-2-carboxylic acid (634-97-9)

pyrrolylmagnesium bromide

pyrrolyllithium

dimethyl pyrrole-1,2-dicarboxylate