A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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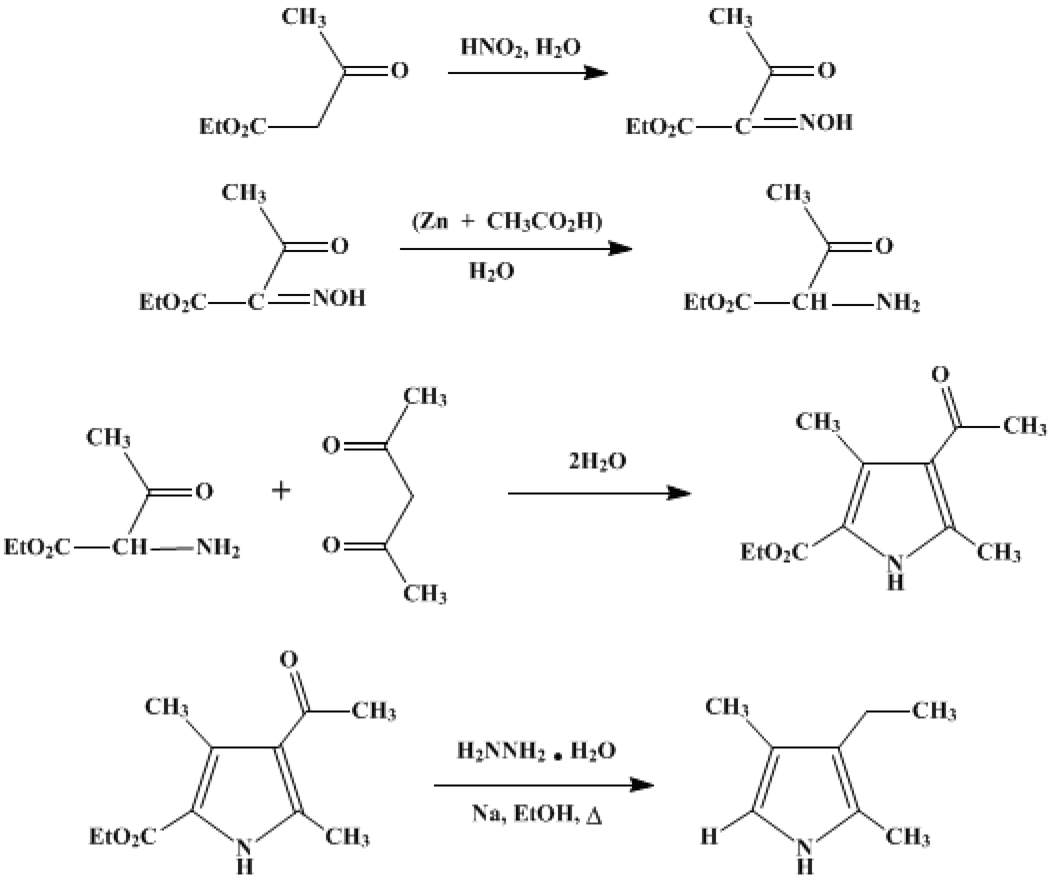
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.021.0067

Organic Syntheses, Coll. Vol. 3, p.513 (1955); Vol. 21, p.67 (1941).

KRYPTOPYRROLE

[Pyrrole, 2,4-dimethyl-3-ethyl]



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1. Procedure

In a 3-l. three-necked flask provided with a stirrer and surrounded by an ice bath are placed 402 g. (3.09 moles) of ethyl acetoacetate (Note 1) and 1.2 1. of glacial acetic acid. To this solution is then added dropwise with stirring a solution of 246 g. (3.55 moles) of sodium nitrite in 400 ml. of water. The rate of addition is controlled so that the temperature does not rise above 12°. After the sodium nitrite solution has been added, the mixture is stirred an additional 2–3 hours. It is then allowed to warm up to room temperature and stand about 12 hours, after which 348 g. (3.48 moles) of acetylacetone is added at one time.

To the reaction mixture 450 g. of zinc dust (Note 2) is added in portions of about 10 g. with vigorous stirring. The rate of addition is regulated so that the temperature never rises above 60°. After the addition is complete (Note 3), the mixture is refluxed for 2–3 hours on a hot plate until the unreacted zinc dust collects in balls. The hot solution is then poured through a fine copper sieve, with stirring, into 30 l. of ice water. The crude product which separates is contaminated with zinc (Note 4). On recrystallization from 1.5 l. of 95% ethanol, 360–390 g. of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole (m.p. 143–144°) is obtained (55–60% based on the ethyl acetoacetate used) (Note 5). A second recrystallization may be necessary to secure a perfectly white product, but the product of the first recrystallization is sufficiently pure for conversion to kryptopyrrole.

Thirty grams of sodium is dissolved in 430 ml. of absolute ethanol, the last protions by heating under reflux. The hot ethanolic solution is poured into an autoclave (Note 6), 75 g. (0.36 mole) of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole is stirred in, and 36 ml. of hydrazine hydrate (Note 7) is added. The autoclave is then heated and the mixture kept at 165–170° for 12 hours. After being cooled, the contents of the autoclave are emptied into a 2-l. round-bottomed flask. The autoclave is rinsed with a small amount of absolute ethanol, and these washings are added to the 2-l. flask. Then 50 ml. of water is added, and the ethanol is distilled from a steam bath, followed by steam distillation of the kryptopyrrole. The ethanolic distillate is collected separately. A glass condenser should be used for the steam distillation, as in some runs a white solid which melts around room temperature begins to appear after about 1 l. has distilled. The condenser water is turned off periodically to allow the solid in the condenser to melt. Steam distillation is continued until the drops of distillate are no longer cloudy, that is, after about 1.7 l. has distilled. A slow stream of nitrogen is passed over the surface of the distillate during the steam distillation (Note 8).

The ethanolic distillate is diluted to 2 l. with distilled water and extracted with a 500-ml. and then a 300-ml. portion of ether. The steam distillate is extracted twice with this ether extract, and twice more with 250-ml. portions of fresh ether. The ether extracts are combined and dried with 150 g. of anhydrous sodium sulfate. The space above the solution is filled with nitrogen. The ether solution is decanted, and the sodium sulfate is washed three times with distilled ether. The ether is then distilled, the temperature of the bath about the flask being raised finally to 130°. The kryptopyrrole is then fractionated under reduced pressure (Note 9). The yield of water-white product boiling within a 1.5° range (85.5–87°/12.5 mm.; 92.5–94° /18 mm.) is 22–25.5 g. (50–58%).

2. Notes

1. The ester used was a commercial product and was not further purified.
2. The zinc dust should be at least 80% pure.
3. Before the reaction mixture is refluxed, enough time should be allowed for the zinc dust to react completely; otherwise considerable trouble with foaming may be encountered.
4. The crude pyrrole darkens on exposure to light, especially when exposed to direct sunlight. The recrystallized product is unaffected by light.
5. The preparation can be carried out in larger or smaller quantities with proportionate amounts of materials and volumes of containers without affecting the yield. The amounts specified here are 60% of those used by the submitter.
6. The checkers used a steel hydrogenation bomb with a void of 650 ml. from which the inside bent steel tube leading to the gauge assembly was removed. A steel plug was inserted in the opening which usually carries a gauge. The temperature was controlled by an automatic regulator, and the reaction mixture was not shaken or stirred.
7. Hydrazine hydrate may be prepared by the ammonolysis of hydrazine sulfate,[1] followed by the addition of water.

Liquid ammonia is placed in a 1-pint thermos bottle, and 60 g. of Eastman's hydrazine sulfate is added in small portions while the liquid is stirred mechanically. After the addition is complete, stirring is continued for 30 minutes. The mixture is filtered into another thermos bottle through a fluted filter paper, and the remaining solid is washed twice with liquid ammonia by transferring it back to the original flask, stirring, and again filtering. On evaporation of the liquid ammonia 7.5–10 g. of colorless liquid is left, 51–68% calculated as anhydrous hydrazine. Five milliliters of water is then added. Three to four such runs are required to obtain the hydrazine hydrate needed in this preparation.

8. Kryptopyrrole is very sensitive to oxidation and should be handled with a minimum amount of exposure to the air. It is best stored in sealed glass tubes. If a capillary ebullition tube is used during distillation under reduced pressure, the tube should be connected to a supply of nitrogen.
9. A Vigreux, a modified Widmer, or other column may be used for this separation.

3. Discussion

Kryptopyrrole has been obtained by the degradation of bilirubin, hemin, rhodoporphyrin, etc.[2] The synthesis given above is based upon the work of Knorr and Hess.[3]

References and Notes

1. Browne and Welsh, *J. Am. Chem. Soc.*, **33**, 1728 (1911).
2. Fischer-Orth, *Die Chemie des Pyrrols*, p. 53, Akademische Verlagsgesellschaft, Leipzig, 1934.
3. Knorr and Hess, *Ber.*, **44**, 2765 (1911).

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

HEMIN

Kryptopyrrole

bilirubin

rhodoporphyrin

ethanol (64-17-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

zinc (7440-66-6)

sodium (13966-32-0)

hydrazine hydrate (7803-57-8)

Ethyl acetoacetate (141-97-9)

Hydrazine sulfate (10034-93-2)

hydrazine (302-01-2)

Acetylacetone (123-54-6)

Pyrrole, 2,4-dimethyl-3-ethyl (517-22-6)

2,4-Dimethyl-3-acetyl-5-carbethoxypyrrole (2386-26-7)