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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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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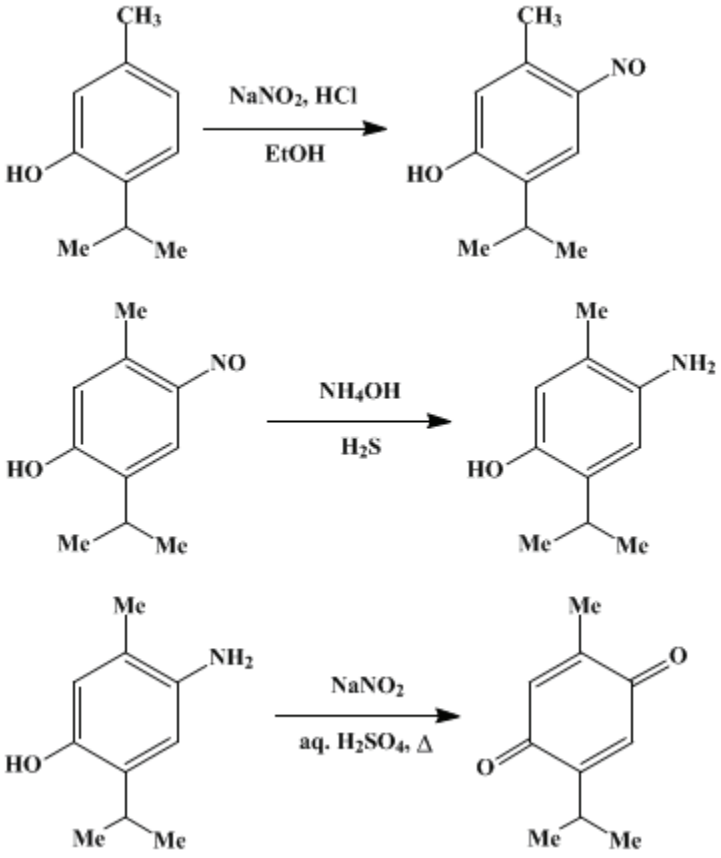
THYMOQUINONE



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1. Procedure

(*A*) *Nitrosothymol*.—To a solution of 100 g. (0.66 mole) of thymol in 500 cc. of 95 per cent ethyl alcohol is added 500 cc. of concentrated hydrochloric acid. This mixture is cooled to 0° in a 2-l. beaker set in an ice-salt bath, and to it is added 72 g. (1 mole) of commercial sodium nitrite in portions of about 5 g. each.

The mixture is stirred well after each addition (Note 1). The solution first becomes brown in color, and a green precipitate soon begins to form. After 35 g. of nitrite has been added, the mixture becomes pasty; the intervals between the additions must now be lengthened and the stirring made more vigorous. When all has been added, the bulk of the product is transferred to a 12-l. flask containing 8 l. of cold water, and the remainder washed in with water. The product, after agitation with water, is now a light-yellow, fluffy solid; it is filtered off by suction and washed well with water (Note 2).

(*B*) *Aminothymol*.—The crude, wet nitrosothymol so obtained is worked up with a mixture of 900 cc. of 28 per cent aqueous ammonia (sp. gr. 0.90) and 1600 cc. of water; the brown solution is filtered free of a little resinous matter, and hydrogen sulfide is passed into it. The brown color disappears and a white precipitate of aminothymol forms. The passage of hydrogen sulfide is continued for thirty minutes longer (Note 3), when the base is filtered and washed well with cold water, contact with air being avoided as far as possible (Note 4).

(*C*) *Thymoquinone*.—The wet aminothymol thus prepared is immediately dissolved in 110 cc. of concentrated sulfuric acid diluted to 4 l. and contained in a 12-l. flask. To this solution is added 150 g.

(2.08 moles) of sodium nitrite, in 5–10 g. portions, with shaking after each addition. The resulting mixture is heated to 60° on a steam bath, with occasional shaking, for one-half hour (Note 5), and is then distilled in a current of steam, by means of the apparatus described on p. 479 (Note 6). All the thymoquinone passes over with the first 3 l. of distillate; it solidifies on cooling, and is filtered with suction (Note 7), washed, and dried at room temperature. The yield is 80–87 g. (73–80 per cent of the theoretical amount) of bright yellow crystals, melting at 43–45° (Note 8).

2. Notes

1. No nitrous acid escapes from the mixture, since it is converted into ethyl nitrite which in turn reacts with the thymol.
2. The crude nitrosothymol may be purified by drying and subsequent recrystallization from 2 l. of benzene, from which it separates as a pale yellow solid, melting at 160–164°. A small second crop is obtained on concentrating the mother liquor, which contains in addition an orange-colored resinous impurity. The yield is 103 g. (87 per cent of the theoretical amount).
3. If the base is filtered off without passing in the excess of hydrogen sulfide, it immediately assumes a purple color on exposure to air.
4. The free base tends to become oxidized in the air but may be preserved as the hydrochloride. This is prepared by transferring it as soon as possible to 1500 cc. of distilled water containing 100 cc. of concentrated hydrochloric acid. The sparingly soluble hydrochloride separates at once. It is recrystallized from the mixture with the use of a little decolorizing carbon, whereupon it separates as colorless needles. A further crop is obtained on concentrating the mother liquor under reduced pressure to about 200 cc. The yield is 110 g. (82.1) per cent of the theoretical amount).
5. The greater part of the oxides of nitrogen escapes during this treatment; the small amount that passes over with the thymoquinone does not harm the product.
6. If an ordinary condenser is employed for the steam distillation, care must be taken that the distilled product does not crystallize in the condenser tube and clog it.
7. The watery filtrate contains about 0.5 g. of dissolved thymoquinone; this can be recovered by distilling over 500 cc. of it and filtering the distillate.
8. The melting point is not appreciably raised by recrystallization from petroleum ether (b.p. 60–80°).

3. Discussion

Thymoquinone can be prepared directly from thymol by sulfonating and oxidizing the sulfonation mixture with manganese dioxide[1] or potassium dichromate;[2] the same process has been successfully employed with carvacrol.[3] The oxidation of salts of aminothymol with dichromate,[4] ferric chloride,[5] or nascent bromine[6] leads to satisfactory yields of thymoquinone, as does prolonged refluxing of nitrosothymol with dilute hydrochloric acid.[7] The procedure described is based on the observation[8] that the diazonium salt obtained from aminothymol is almost quantitatively converted into thymoquinone on warming in the presence of excess nitrous acid.

References and Notes

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

oxides of nitrogen

petroleum ether

salts of aminothymol

nascent bromine

diazonium salt obtained from aminothymol

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

hydrogen sulfide (7783-06-4)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

nitrite (14797-65-0)

decolorizing carbon (7782-42-5)

manganese dioxide (1313-13-9)

ferric chloride (7705-08-0)

ethyl nitrite (109-95-5)

potassium dichromate (7778-50-9)

Thymoquinone (490-91-5)

Nitrosothymol (2364-54-7)

thymol (89-83-8)

Aminothymol

carvacrol (499-75-2)