Organic Syntheses

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.

DIETHYL *trans*-Δ⁴-TETRAHYDROPHTHALATE

[4-Cyclohexene-1,2-dicarboxylic acid, diethyl ester, *trans*-]
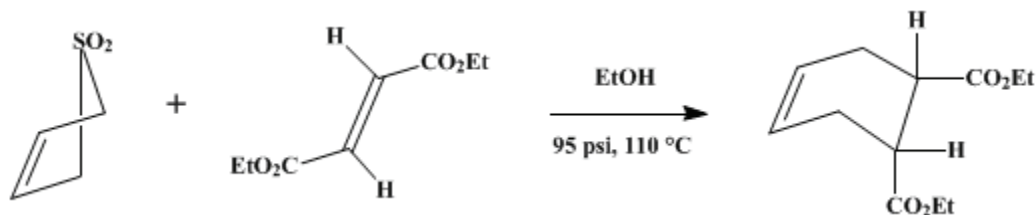
Submitted by Thomas E. Sample, Jr.[1] and Lewis F. Hatch[2].
Checked by Elaine Dotter Donald and Richard E. Benson.

1. Procedure

A 300-ml. pressure reaction vessel, capable of withstanding at least 250 p.s.i. at 125° (Note 1) is charged with 60.0 g. (0.508 mole) of 3-sulfolene (Note 2), 86.0 g. (82.0 ml., 0.500 mole) of diethyl fumarate (Note 3), and 1.0 g. of hydroquinone (Note 4). Commercial absolute ethanol (90 ml.) is added, and the mixture stirred until most of the solid is dissolved. The vessel is sealed, heated slowly to 105–110° (Note 5), and maintained at that temperature 8–10 hours (Note 6). The vessel is then allowed to cool to room temperature, opened (Note 7), and the yellowish, fluid reaction mixture is poured into a 1-l. Erlenmeyer flask.

The liquid is stirred vigorously (Note 8), and a solution of 60.0 g. (0.566 mole) of sodium carbonate in 350 ml. of water is added to the flask as rapidly as the concomitant evolution of carbon dioxide will permit. Stirring is continued for about 15 minutes after the addition is complete. The original reaction vessel is rinsed with 200 ml. of petroleum ether (b.p. 60–75°) (Note 9), the rinse is added to the Erlenmeyer flask containing the product, and the mixture is stirred for about 10 minutes at a rate sufficient to achieve homogenization. The resulting loose emulsion is quickly transferred to a 1-l. separatory funnel and allowed to separate; the lower (aqueous) phase is drawn off into the original Erlenmeyer flask and the upper (organic) layer containing the desired product is transferred to a 500-ml. flask. In exactly the same manner the aqueous phase is extracted by vigorous stirring with two 100-ml. portions of petroleum ether, the organic layers being added to the retention flask (Note 10). The combined organic layers are transferred from the flask to the same separatory funnel and shaken once with 100 ml. of cold, 5%, aqueous sodium carbonate and twice with 50-ml. portions of cold water. The organic layer is returned to the retention flask, dried over 10 g. of anhydrous magnesium sulfate, filtered by gravity, concentrated with a rotary evaporator (Note 11), and distilled under reduced pressure through a Vigreux column, yielding 75–82 g. (66–73%, based on diethyl fumarate) of the product, b.p. 129–132° (5 mm.), n_D^{25} 1.4565–1.4570, d_4^{25} 1.0584–1.0589 (Note 13).

2. Notes

1. The maximum static pressure developed at 110°, measured by the submitters, never exceeded 95 p.s.i.; however, for most of their runs they used stainless or carbon steel autoclaves with screw-on covers rated for service up to 500 p.s.i. at 250° (medium-pressure catalytic hydrogenation bombs). Gaskets or inner-disk seals for the autoclave covers were cut from soft thin copper sheet stock instead of the more usual lead or lead-alloy material. Whereas use of lead-containing seals did not seem to affect the yields, when they were used the product invariably had the offensive odor of divalent organic sulfur which was still noticeable after final distillation; substitution of copper seals eliminated this problem completely. Close-fitting, removable glass liners for the autoclave were used by the submitters for convenience in weighing and mixing the charge, and for subsequent removal of the product mixture, but are not required. Several runs were made at 100–105° by the submitters, without difficulty, utilizing a hydrogenation bottle of heavy borosilicate glass tightly closed with a clamped-in Neoprene stopper and

placed inside an iron sleeve for safety.

2. 3-Sulfolene (butadiene cyclic sulfone), m.p. 64–66°, from Shell Chemical Co., or from Aldrich Chemical Co., was found satisfactory for use as received. One lot purchased from another source required solution in hot methanol and treatment with activated carbon (250 ml. of methanol and 2 g. of Norit per 100 g. of material), filtration, and crystallization to free it of color, odor, and particulate matter.

3. Diethyl fumarate from Aldrich Chemical Co., n_D^{20} 1.4406, b.p. 97.5–97.7° (10 mm.), was employed without treatment.

4. Eastman Kodak Co. hydroquinone, m.p. 172–174°, was used. 4-tert-Butylcatechol, m.p. 38–42°, from the same supplier, proved to be an equally effective polymerization inhibitor.

5. The submitters used an ordinary hot-air oven with the usual simple bimetallic temperature regulator for the majority of their experiments. In several instances, however, a large oil bath regulated with a thermostat to within ±1.0° was employed, which, in providing more exact control of the total temperature environment of the reaction, gave a greater degree of reproducibility in product yield between successive runs at any set temperature; these precise runs were performed as a result of the checkers' observations emphasizing the important effect of reaction temperature on yields.

6. Longer heating periods (12–18 hours) were found by the submitters to elevate the yields only slightly. On the other hand, as the checkers noted, heating for the recommended 8–10 hours at temperatures above 110° will raise the yields quite significantly: the highest single product recovery obtained by the submitters was 86.8% using a strong steel autoclave (Note 1) immersed for 10 hours in a thermostat-equipped oil bath at 125°. However, the greater yield which may be realized through higher reaction temperatures should be carefully weighed against the ability of the reaction vessel to contain safely the greater pressures developed.

7. Little, if any, overpressure is released if the vessel is opened below 30°; this should be done in a hood because the contents will evolve sulfur dioxide until the sodium carbonate is added.

8. A magnetic stirrer is recommended for this operation.

9. Hexane and Skellysolve-B serve equally well; the product is miscible with aliphatic solvents, whereas 3-sulfolene is not.

10. No increase in product recovery was observed by the submitters when a 72-hours exhaustive extraction of the neutralized reaction mixture with hexane in a continuous apparatus was substituted for the procedure described.

11. The submitters observe that no more critical step in this procedure exists than the efficient removal of the rather large quantity of solvent from the product before distillation: entrainment losses during this operation usually were found chiefly responsible when the synthesis gave a low yield (recovery). The preferred apparatus for this step is a rotary evaporator equipped with a long, helical, water-cooled condenser; the distillation flask is attached to the evaporator and the product solution added portionwise as the concentration progresses; the temperature of the flask is held at 30–40° with a warm-water bath, or a heat lamp, while the solvent is gently removed by a water aspirator (ca. 30-mm. minimum pressure). If a suitable rotary evaporator is unavailable, a 30–45 cm. Vigreux column may be used without excessive product loss, providing the flask is warmed in the same manner and a gentle boiling rate is maintained through control of the aspirator suction.

12. An elaborate apparatus for the diminished-pressure distillation is not required to obtain a product of excellent purity: sensitive GC analyses could detect no more than a doubtful trace of the cis isomer in the crude mixture, and other possible contaminants boil at least 45° (760 mm.) below the product. The submitters usually employed an 8 × 300 mm., vacuum-jacketed, silvered column with a helical, Nichrome-wire heat transfer insert. They consistently obtained a product which analyzed at least 99% pure using GC conditions which proved capable of cleanly separating the product from an authentic sample of its cis-isomer [Org. Synth., **Coll. Vol. 4**, 304 (1963)], with the latter showing the longer retention time (terephthalic acid-terminated Carbowax 20M, 10% w/w on 60/80 mesh Chromosorb W, 6 mm. × 365 cm. aluminum column at 150°). The submitters note that distillation of the product at atmospheric pressure (b.p. 265–270°) is accompanied by very slight decomposition. (A b.p. of 150.5–151.5° at an unspecified pressure appears in the literature.[3])

13. The IR spectra of diethyl trans-Δ⁴-tetrahydrophthalate and its cis-isomer [Org. Synth., **Coll. Vol. 4**, 304 (1963)], (cm⁻¹, neat liquids purified by GC, 0.025-mm. cells) are similar in the fundamental region; however, the following particular absorptions in the "fingerprint" region afford reliable analytical criteria for distinguishing each from (or in the presence of) the other; trans-isomer, 971 (s), 755, 743 (m,

s, doublet); *cis*-isomer, 945 (s), 893 (w), 727 (m). The 755, 743 doublet of the *trans*-isomer and the 727 single absorption of the *cis*-isomer appear to be characteristic, and related to out-of-plane deformations of the vinylic hydrogens; bands corresponding to the 971 and 755, 743 absorptions of the *trans*-isomer are present also in the spectrum of dimethyl *trans*-Δ^4-tetrahydrophthalate.[4]

3. Discussion

A report of Backer and Blaas[5] is responsible for evolution of the present procedure; these workers were first to conduct a Diels-Alder synthesis utilizing a 3-sulfolene in place of the free diene (by heating the cyclic adduct of sulfur dioxide and 2-methyl-3-thiomethyl-1,3-butadiene with maleic anhydride). The generality of the method as a variant of the conventional diene synthesis is limited largely by the availability of the appropriate 3-sulfolene; its greatest utility, perhaps, will be realized in those diene reactions normally requiring 1,3-butadiene, since 3-sulfolene itself is now the least expensive and most widely available diene cyclic sulfone.

The submitters, in addition to their successful work with 3-sulfolene itself, have generally obtained very satisfactory results performing diene syntheses based on the present procedure using several fumaric and maleic derivatives (notably fumaric acid and fumaronitrile, and diethyl maleate) in conjunction with 3-methyl-3-sulfolene (isoprene cyclic sulfone)[6] and 2,4-dimethyl-3-sulfolene (available from Aldrich Chemical Co.), as well as 3,4-dimethyl-3-sulfolene.[7]

In preparations wherein the dienophile could undergo side reaction with the solvent alcohol, either benzene or toluene usually proved to be a satisfactory reaction medium; lower-boiling solvents, such as ether, chloroform, or acetone, were avoided by the submitters because of the high reactive pressures developed. If the dienophile is highly reactive and not appreciably volatile below about 200°, the reaction may be successfully conducted without solvent by careful fusion of an intimate mixture of the reactants in an open vessel.[5,8] *Caution! Such fusions should be performed in a good fume hood because of the copious evolution of sulfur dioxide.*

3-Sulfolene as an alternative reactant for 1,3-butadiene in diene syntheses has the following advantages: it presents no particular flammability hazard[9] and is practically nontoxic;[10] it is an odorless, crystalline, nonhygroscopic solid which may be stored without inhibitor at ordinary temperatures for years with no evidence of deterioration;[10] obviously, no low-temperature liquefication procedures are needed for its handling, as butadiene may require; medium-pressure reaction vessels can be safely employed since autogenous pressures are relatively low owing to the thermally controlled release of the 1,3-butadiene;[11] and, because the substantial excess of free diene often employed to force the usual reaction is not required, formation of troublesome polymeric by-products is greatly diminished.

For the preparation of diethyl *trans*-Δ^4-tetrahydrophthalate, the present synthesis is superior to the Diels-Alder reaction of butadiene with diethyl fumarate[3] for the reasons given above. In addition, a higher yield is obtained at a lower reaction temperature and shorter reaction time.

Whereas *cis*-Δ^4-tetrahydrophthalic anhydride and several of its derivatives are readily available in high purity from a number of suppliers (largely because of the great ease of addition of maleic anhydride to 1,3-butadiene),[12] the *trans* analogs are much more difficult and expensive to prepare and isolate in reasonable yields and purity; hence the latter are rarely procurable at present from the usual laboratory supply sources. Thus, the procedure described for the preparation of highly pure diethyl *trans*-Δ^4-tetrahydrophthalate not only illustrates a useful variation of the diene synthesis, but provides a convenient route to a large number of *trans*-1,2-disubstituted cyclohexyl derivatives that are currently difficult to secure and are of importance for a variety of studies concerned with structural problems.

References and Notes

1. Texaco Inc., Bellaire Research Laboratories, Bellaire, Texas 77401 [Present address: Magcobar Division, Dresser Industries, Inc., 10205 Westheimer Road, Houston, Texas 77042.]
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Chemistry at The University of Texas, Austin, Texas 78712.

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

petroleum ether

Isoprene cyclic sulfone

cis-Δ^4-Tetrahydrophthalic anhydride

Diethyl trans-Δ^4-tetrahydrophthalate

butadiene cyclic sulfone

dimethyl trans-Δ^4-tetrahydrophthalate

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

hydroquinone (123-31-9)

iron (7439-89-6)

sodium carbonate (497-19-8)

sulfur dioxide,
sulfone (7446-09-5)

sulfur (7704-34-9)

carbon dioxide (124-38-9)

copper (7440-50-8)

acetone (67-64-1)

carbon,
Norit (7782-42-5)

toluene (108-88-3)

Fumaric acid (110-17-8)

diethyl fumarate (623-91-6)

diethyl maleate (141-05-9)

magnesium sulfate (7487-88-9)

1,3-Butadiene,
butadiene (106-99-0)

maleic anhydride (108-31-6)

3-methyl-3-sulfolene (1193-10-8)

hexane (110-54-3)

Fumaronitrile (764-42-1)

3-sulfolene

2-methyl-3-thiomethyl-1,3-butadiene

2,4-dimethyl-3-sulfolene

3,4-dimethyl-3-sulfolene

4-tert-butylcatechol (98-29-3)

4-Cyclohexene-1,2-dicarboxylic acid, diethyl ester, trans- (5048-50-0)