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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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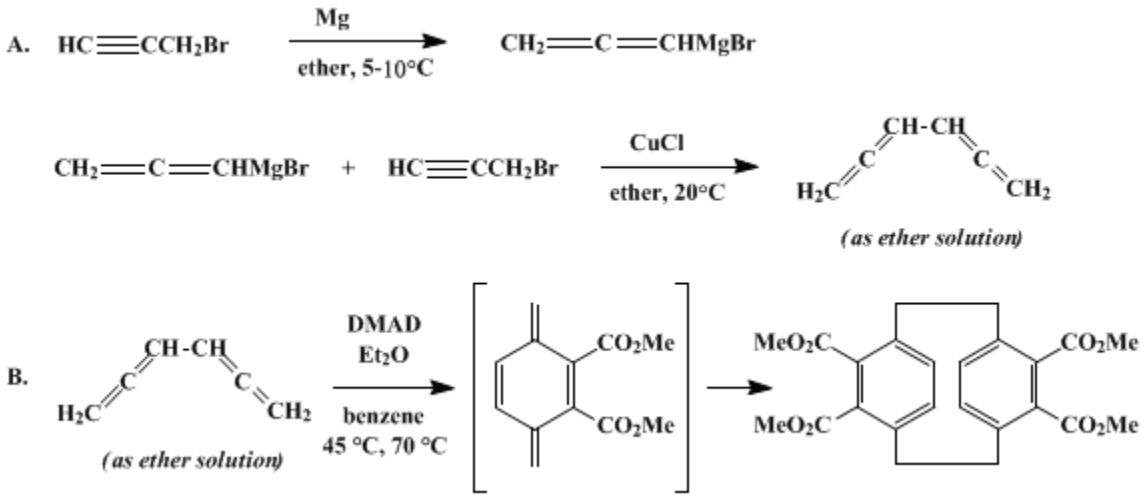
DIELS-ALDER REACTION OF 1,2,4,5-HEXATETRAENE: TETRAMETHYL[2.2]PARACYCLOPHANE-4,5,12,13-TETRACARBOXYLATE

[Tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene-5,6,11,12-tetracarboxylic acid, tetramethyl ester]



Submitted by Henning Hopf, Ingrid Böhm, and Jürgen Kleinschroth[1].
Checked by Paul F. Sherwin and Robert M. Coates.

1. Procedure

Caution! Propargyl bromide is poisonous and should be handled in a well-ventilated hood. Benzene has been identified as a carcinogen; OSHA has issued emergency standards for its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *1,2,4,5-Hexatetraene in ether solution*. A 2-L, four-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser fitted with a drying tube containing anhydrous calcium sulfate (Drierite), a dropping funnel, and a thermometer (Note 1). The flask is charged with 0.5 g (0.002 mol) of mercury(II) chloride and 29.2 g (1.2 mol) of magnesium turnings that have been crushed with a mortar and pestle, and the apparatus is flushed with nitrogen while being heated externally with a Bunsen burner to remove traces of moisture. In the cooled flask are placed 160 mL of anhydrous ethyl ether (Note 2) and 7.6 g (5.0 mL, 0.064 mol) of propargyl bromide (Note 3). The ether begins to reflux within 1 min, indicating that formation of the Grignard reagent has begun (Note 4). The mixture is cooled to 5° in an ice-salt bath and stirred vigorously as a solution of 135 g (89 mL, 1.13 mol) of propargyl bromide in 560 mL of anhydrous ether is added. The addition rate is adjusted so as to maintain the internal temperature between 5°C and 10°C (Note 5). The cooling bath is removed, and the dark green mixture is stirred for 45 min at room temperature (Note 6). A 2-g (0.02 mol) portion of finely pulverized, dry copper(I) chloride (Note 7) is added, and the mixture, which becomes a chocolate-brown color after 2–3 min, is stirred for 15 min at room temperature and cooled again to 5°C with either an ice-water bath or an ice-salt bath. Stirring is continued while a solution of 128 g (85 mL, 1.08 mol) of propargyl bromide in 100 mL of ether is added at a rate such that the internal temperature is kept at ca. 20°C (Note 8). The mixture becomes almost black, and two phases are discernible when the stirrer is stopped, especially toward the end of the addition. The cooling bath is removed and stirring is continued for 15 min at room temperature to complete the dimerization. The reaction mixture is cooled to 0°C

with an ice-salt bath and stirred vigorously as 200 mL of 1 *N* aqueous hydrochloric acid is added (Note 9). The two-phase mixture is warmed to room temperature, and another 100 mL of 1 *N* hydrochloric acid is added. The ether layer is separated and washed with three 100-mL portions of water (Note 10). A few crystals (0.2–0.5 g) of hydroquinone are added to stabilize the reddish solution, which is then dried with anhydrous potassium carbonate. The drying agent is filtered, and the filtrate is concentrated to a volume of ca. 400 mL by distillation under nitrogen at atmospheric pressure with a 40-cm Vigreux column and a heating bath kept at 40–45°C. The concentrate is purified by vacuum transfer (Note 11), and the now colorless solution, which contains ca. 25–30 g (30–36%) of 1,2,4,5-hexatetraene, is stabilized by adding another 0.1–0.5 g of hydroquinone (Note 12) and (Note 13).

B. *Tetramethyl[2.2]paracyclophane-4,5,12,13-tetracarboxylate*. The 1-L flask from Step A containing ca. 25–30 g (0.32–0.38 mol) of 1,2,4,5-hexatetraene in ether solution is equipped with a magnetic stirring bar and a 40-cm Vigreux column for distillation at atmospheric pressure. A solution of 69.4 g (60 mL, 0.49 mol) of dimethyl acetylenedicarboxylate (Note 14) in 220 mL of benzene (Note 15) is added. The resulting solution is stirred and heated at 45°C for 5–7 hr and at 70°C for 20 hr (Note 16). The ether distils slowly at 45°C and rather rapidly at 70°C, the color of the solution changes from yellow to red–orange, and a white solid is gradually deposited. The mixture is cooled and filtered. Recrystallization of the solid from 600–800 mL of toluene affords 27–35 g of white crystalline product, mp 201.5–203°C. The original benzene filtrate and the toluene mother liquor, when evaporated to dryness and crystallized separately from 40–70 mL of toluene, provide 3–4 g and 2–3 g of product, respectively, having essentially the same melting point. The combined yield is 33–41 g (40–50% based on 1,2,4,5-hexatetraene) (Note 17) and (Note 18).

2. Notes

1. The checkers used a three-necked flask equipped with a Claisen adapter. The straight branch of the adapter was fitted with a thermometer, and the curved branch was mounted with a condenser bearing a nitrogen inlet. After the nitrogen-filled apparatus had been flamed dry and cooled, the dropping funnel was capped with a rubber septum. A nitrogen atmosphere was maintained in the apparatus at all times, and liquids were placed in the dropping funnel via syringe.
2. The checkers dried the ether by distillation from sodium benzophenone ketyl immediately before use.
3. Propargyl bromide may be purchased from Fluka. The reagent may also be prepared by the procedure of Gaudemar.[2] Propargyl bromide (97%) supplied by Tridom Chemical Inc. was dried by the checkers prior to use by stirring over Linde-type 4A molecular sieves under a nitrogen atmosphere for 2–3 days. The volumetric quantities given in the procedure are for 97% propargyl bromide, which has a density of 1.56 at 20°C according to a catalog from Tridom Chemical Inc.
4. The submitters initiated Grignard formation by adding a few milliliters of a solution of 142.8 g (1.2 mol) of propargyl bromide in 560 mL of anhydrous ether. If the reaction does not begin, they suggest that the flask be heated with a warm stream of air from a "heat gun."
5. The checkers found that the addition time varied from ca. 1 to 4 hr, depending on the temperature of the cooling bath and the extent to which it was stirred.
6. Some unreacted magnesium turnings remain in the flask at this time. However, the submitters recommend against heating the mixture to achieve further conversion, since the initially formed allenylmagnesium bromide will isomerize to 1-propynylmagnesium bromide.
7. The submitters used copper(I) chloride purchased from E. Merck, Darmstadt, which had a greenish tinge attributed to slight contamination by copper(II) salts. The reagent used by the checkers was supplied by J. T. Baker Chemical Company.
8. The checkers, using an ice-salt cooling bath, maintained the internal temperature between 7°C and 12°C. The addition time varied from 15 to 75 min depending on the efficiency of the cooling.
9. The internal temperature was maintained at 10–15°C by the submitters and 5–12°C by the checkers. The time required for the hydrolysis was reduced by the checkers by prior chilling of the hydrochloric acid.
10. Since the product is unstable to oxygen, the checkers tried to keep the ethereal solution under a nitrogen atmosphere during transfer and extractions.
11. The crude solution of 1,2,4,5-hexatetraene may also be employed in part B. However, yields are lower, and the purification of the product becomes tedious owing to the presence of insoluble by-products. The vacuum transfer may be accomplished with a simple distillation apparatus equipped with

a magnetic stirring bar and a 1-L, round-bottomed flask as receiver in the following manner. The crude ethereal solution is chilled to a glass with a liquid nitrogen bath, and the apparatus is evacuated to a pressure of 1–3 mm with a vacuum pump. The apparatus is isolated from the vacuum pump, the cooling bath is removed, and the ether glass is allowed to warm until it becomes mobile. The freeze–evacuate–thaw cycle is repeated two more times to complete the degassing process. The solution is again chilled with liquid nitrogen, the apparatus is evacuated to 1–3 mm, and the system is then isolated from the vacuum pump. The receiving flask is cooled with a liquid nitrogen or dry ice-isopropyl alcohol bath, the cooling bath is removed from the distilling flask, and the ether solution is stirred and allowed to warm to room temperature in the closed system. Once the ether solution becomes mobile, the flask may be warmed cautiously with a water bath at room temperature to speed up the vacuum transfer.

12. Pure 1,2,4,5-hexatetraene polymerizes readily when exposed to air at room temperature. However, solutions of the purified compound are stable for months at 0°C, especially if protected by an inert gas. Contact with air should be minimized to avoid inducing polymerization.

13. The amount of 1,2,4,5-hexatetraene in solution was estimated by the submitters from ^{1}H NMR spectra and GC analyses. The major product of the dimerization reaction is 1,2-hexadien-5-yne. The submitters have shown that this hydrocarbon does not interfere with the cycloaddition in Step B.

14. Dimethyl acetylenedicarboxylate is supplied by Aldrich Chemical Company, Inc.; E. Merck, Darmstadt; and Fluka. The reagent, bp 110–112°C (15 mm), was distilled before use.

15. The checkers carried out one run on one-tenth scale using toluene instead of benzene in part B. The yield of tetramethyl[2.2]paracyclophane-4,5,12,13-tetracarboxylate, mp 202.5–204°C, was 2.91 g (35% based on 1,2,4,5-hexatetraene in part A).

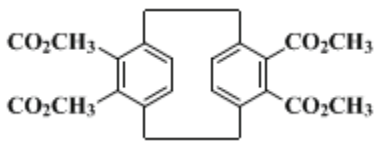
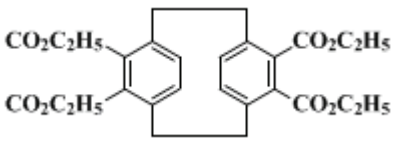
16. The conditions and isolation procedure given are those used by the checkers. The submitters heated the solution first to 45°C, after which the temperature was gradually increased to 70°C over several hours. The solution was then heated at 70°C overnight, and the solvents were removed by rotary evaporation. The semisolid, yellow-orange residue was recrystallized from benzene or methanol. Concentration of the mother liquor afforded additional crops of crystalline product. The total yield of the tetraester was 25–30 g (30–36% based on 1,2,4,5-hexatetraene), mp 206–207°C.

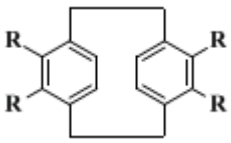
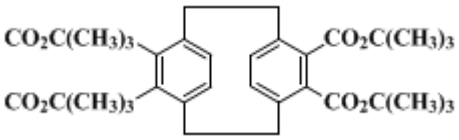
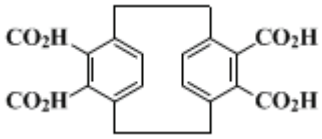
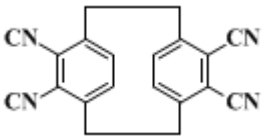
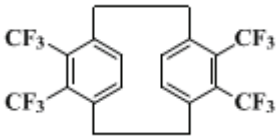
17. The melting point of the product obtained by the checkers increased only slightly to 202–203.5°C on recrystallization from toluene, benzene, or methanol. The once-recrystallized product was analyzed by the checkers. Anal. calcd. for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.51; H, 5.49. The submitters obtained material of analytical purity by sublimation at 180°C (0.001 mm).

The spectral properties of the product are as follows: IR (potassium bromide) cm^{-1}: 1715, 1260, 1195, 1125, 1005, 870; ^{1}H NMR ($CDCl_3$) δ: 2.93–3.43 (nine-line *AA'BB'* multiplet, 8, two CH_2CH_2), 3.83 (singlet, 12, four CO_2CH_3), 6.80 (singlet, 4, four aryl C*H*); proton-decoupled ^{13}C NMR ($CDCl_3$) δ (assignment): 33.27 (CH_2), 52.25 (OCH_3), 131.51 (CCO_2CH_3), 134.98 (CCH_2), 139.68 (*C*H), 168.40 (CO_2CH_3).

TABLE I

[2.2]PARACYCLOPHANES PREPARED BY DIELS-ALDER REACTION OF DISUBSTITUTED ACETYLENES WITH 1,2,4,5-HEXATETRAENE[3], [4]

R	mp (°C)	Yield (%)
CO_2CH_3 	203	47
$CO_2C_2H_5$ 	133.5	30

	$CO_2C(CH_3)_3$ 	205	20
	CO_2H 	365 (dec)	5
	CN 	320 (dec)	37
	CF_3 	174	21

18. The submitters have scaled up this procedure to prepare as much as 60 g of the paracyclophane in one run. However, since the volumes of solvents and flasks are quite large, the operations become rather cumbersome.

3. Discussion

[2.2]Paracyclophanes have been recognized for some time as interesting structures for stereochemical studies and for unusual intra- and intermolecular π-electron interactions.[5]; [6]; [7]; [8]; [9]; [10,11,12,13] The nonplanar, boatlike benzene rings[14] of these compounds have attracted the attention of numerous synthetic organic chemists[5,6,7,8,9,10,11,12,13] as well as theoreticians[15,16] and spectroscopists.[13,17]

The principal methods used previously for the preparation of [2.2]paracyclophanes have been reviewed several times[5,6,7,8,9,10,11,12,13] and include (1) intramolecular Wurtz coupling of appropriately substituted dihalides at high dilution; (2) ring contraction of cyclophanes having larger bridges by sulfone pyrolysis (the most versatile procedure currently known), Stevens rearrangement, and other extrusion reactions; and (3) the dimerization of transient *p*-quinodimethane intermediates (*p*-xylylenes), usually generated from *p*-xylene precursors by elimination reactions.[18] A *p*-quinodimethane is presumably also formed initially in Step B of this procedure. This cycloaddition route to *p*-quinodimethanes and [2.2]paracyclophanes, discovered for the first time in the submitters' laboratories, is attractive on account of the availability of the starting materials, the simplicity of the procedure, and the relatively large quantities of product that may be obtained. The approach appears to be fairly general, since both the bisallene and acetylene components may be varied (Table I).[19,3,4] However, methyl 2-butynoate, 2-butyne, diphenylacetylene, and bistrimethylsilylacetylene failed to react with 1,2,4,5-hexatetraene. Another limitation is the exclusive formation of [2.2]paracyclophanes with the *anti* configuration from disubstituted acetylenic dienophiles.

The substituted [2.2]paracyclophanes prepared by the present procedure have proven to be useful starting materials for the synthesis of cyclophanes with extended aromatic ring systems,[20] additional ethano bridges,[21,22] and chromium tricarbonyl complexes.[23]

References and Notes

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

sodium benzophenone ketyl

TETRAMETHYL[2.2]PARACYCLOPHANE-4,5,12,13-TETRACARBOXYLATE

chromium tricarbonyl complexes

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether,
ethyl ether (60-29-7)

hydroquinone (123-31-9)

magnesium turnings (7439-95-4)

sulfone (7446-09-5)

oxygen (7782-44-7)

nitrogen (7727-37-9)

toluene (108-88-3)

mercury(II) chloride (7487-94-7)

copper(I) chloride (7758-89-6)

Diphenylacetylene (501-65-5)

1-propynylmagnesium bromide

Dimethyl acetylenedicarboxylate (762-42-5)

2-butyne (503-17-3)

propargyl bromide (106-96-7)

1,2,4,5-Hexatetraene (29776-96-3)

allenylmagnesium bromide

1,2-hexadien-5-yne (33142-15-3)

methyl 2-butynoate (23326-27-4)

bistrimethylsilylacetylene (14630-40-1)

p-quinodimethane

Tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene-5,6,11,12-tetracarboxylic acid, tetramethyl ester