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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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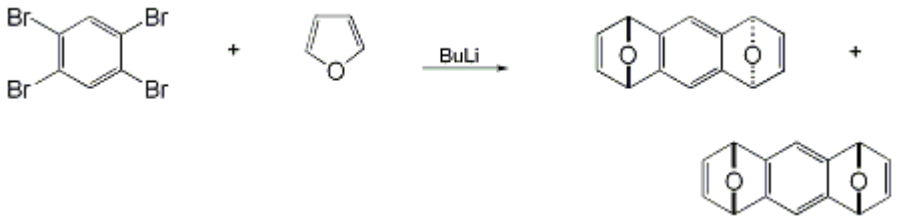
USE OF 1,2,4,5-TETRABROMOBENZENE AS A 1,4-BENZADIYNE EQUIVALENT: anti- AND syn-1,4,5,8-TETRAHYDROANTHRACENE 1,4:5,8-DIEPOXIDES

[1,4:5,8-Diepoxyanthracene, 1,4,5,8-tetrahydro-, (1α,4α,5β,8β)- and (1α,4α,5α,8α)- from benzene, 1,2,4,5-tetrabromo-]



Submitted by Khalil Shahlai, Samuel Osafo Acquaah, and Harold Hart[1] .
Checked by John Leazer and Amos B. Smith, III.

1. Procedure

An oven-dried, 3-L, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a 250-mL pressure-equalizing dropping funnel and an argon inlet is charged with 1500 mL of dry toluene (Note 1), 145 mL (2.0 mol) of freshly distilled furan (Note 2) and 39.4 g (0.1 mol) of 1,2,4,5-tetrabromobenzene (Note 3), (Note 4). In an argon atmosphere, the solution is cooled to −23°C (dry ice, CCl_4) and 131 mL (2.1 equiv) of 1.6 M butyllithium in hexanes (Note 5) is added dropwise over 1 hr. After addition is complete, the mixture is allowed to warm to room temperature (1-2 hr) and is stirred at this temperature for 3 hr. The reaction is quenched by dropwise addition of 10 mL of methanol .

The flask contents are transferred to a separatory funnel, washed with 100 mL of water, 100 mL of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate . The solvent is removed by rotary evaporator and the solid residue is triturated with three portions of cold (0-5°C) methanol (50 mL, then 20 mL twice). The insoluble product is filtered, air dried, and recrystallized from acetone to give as the first crop 3.0-3.4 g of the pure anti isomer (Note 6), (Note 7) mp (dec) > 250°C (Note 8). Additional crystallizations bring the yield to 4.6 g (22%).

The methanol extracts and mother liquor from the final recrystallization of the anti isomer are combined and evaporated to dryness (rotavap). The residue is dissolved in 50 mL of boiling ethyl acetate in a 250-mL Erlenmeyer flask, to which is then added 150 mL of boiling hexanes. The solution is allowed to cool to room temperature and to stand at that temperature for 2-3 hr. Filtration yields the first crop of syn isomer (approximately 3.6 g). Second and third crops of product are obtained by evaporating the mother liquor to dryness and crystallizing the residue from the same solvent mixture (1:3 ethyl acetate/hexanes) (Note 9), to give a total of 5.3 g (25%) of syn isomer, mp 192-194°C (Note 10), (Note 11).

2. Notes

1. Toluene was distilled from sodium metal. The checkers used HPLC grade toluene as received.
2. Furan was distilled over anhydrous potassium carbonate. Excess furan is necessary to trap the aryne intermediates.
3. 1,2,4,5-Tetrabromobenzene used from sources other than Lancaster Synthesis contained trace amounts of an impurity that carried through the entire reaction scheme. This impurity gave a proton resonance at 1.58 ppm in the starting bromide and in both the syn and anti isomeric products. This impurity could not be removed by column chromatography.
4. All the tetrabromobenzene should be in solution before cooling the mixture. The checkers noted that

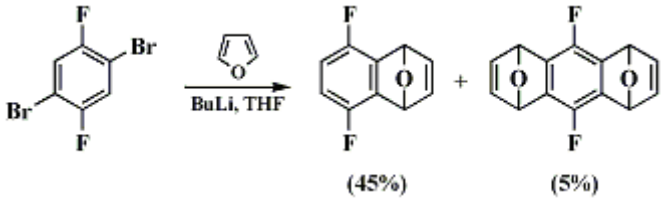
all the tetrabromide did not dissolve even upon prolonged stirring.
5. Butyllithium was purchased from Aldrich Chemical Company, Inc. If fresh, it may be used directly without titration; otherwise it should be titrated.[2] More dilute and/or more concentrated (i.e., 2.5 M) butyllithium in hexanes can be used without altering the yield.
6. Two additional crystallizations, each preceded by reducing the volume of the mother liquor, give an additional 0.8-1.2 and 0.2-0.4 g of anti isomer. The principal constituent of the final mother liquor is the syn isomer.
7. The purity of the isomers is tested by thin layer chromatography (precoated plastic sheets, 0.2 mm silica gel N-HR/UV_{254}) with 3:2:1 hexanes/dichloromethane/ether as the eluant, developed in an iodine chamber; R_f (anti) = 0.45, (syn) = 0.38. The first crop of anti isomer is nearly free of syn contaminant, but the next crops contain 2-3% of the syn isomer. The ^{1}H NMR spectra of the two isomers are virtually identical: ^{1}H δ: 5.62 (s, 4 H), 7.01 (s, 4 H), 7.18 (s, 2 H) . The syn and anti isomers display slight chemical shift differences in the 125 MHz ^{13}C NMR: anti isomer: 147.84, 143.88, 114.05 and 82.35 ppm; syn isomer: 147.85; 143.56; 113.82 and 82.37 ppm.
8. The anti isomer does not melt, but begins to decompose (gas evolution) just above 250°C.
9. One cannot simply reduce the volume of the mother liquor for the second and third crystallizations because of the changing ratio of the solvents.
10. This product contains small amounts (2-3%) of the anti isomer, which cannot be removed by further recrystallization from these or several other solvent systems. Pure syn product, free of anti isomer, can be obtained by column chromatography over silica gel (230-400 mesh) using the same 3-component eluant as for analysis (Note 7).
11. If, instead of purification by crystallization, the crude anti/syn product mixture is chromatographed directly using the 3-component eluant, it is possible to increase the yield of each pure isomer to approximately 30%.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

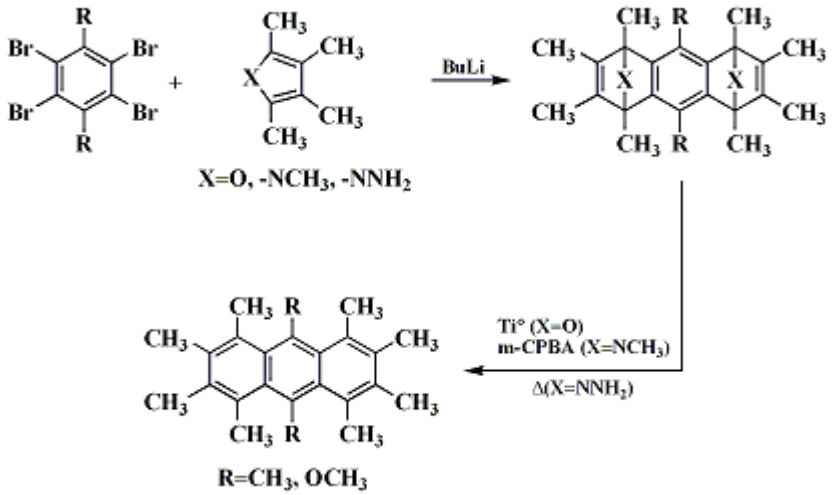
Wittig and Härle were the first to use tetrahaloarenes as diaryne equivalents.[3] From 1,4-dibromo-2,5-difluorobenzene, butyllithium and furan (in THF) they isolated the mono- and bis-adducts shown.



These products obviously arose from metallation at unsubstituted ring positions in the starting tetrahalobenzene. To force metallation at the carbon-bromine bonds, they used 2,6-dibromo-3,5-difluoro-p-xylene which, with magnesium in THF gave mainly mono-adduct. With butyllithium, only the bis-adduct was obtained (15%). No mention was made of syn/anti isomers of the bis-adducts.

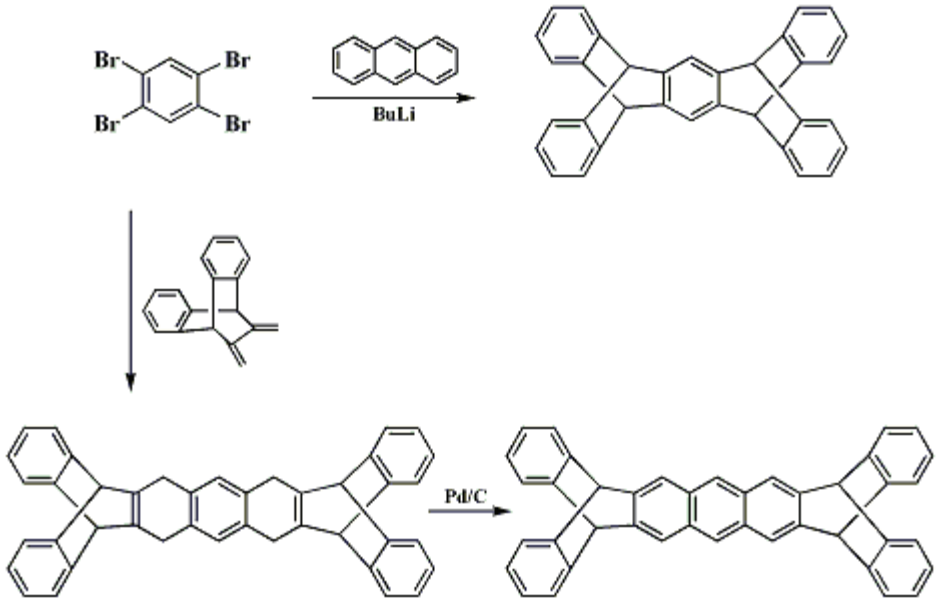
Replacement of the fluorines by bromines,[4,5] as in the procedure described here, resulted in several major improvements that made the reaction synthetically useful: (a) ring metallation is completely suppressed, (b) the starting material is either commercially available, as in the present example, or much more easily synthesized than corresponding fluorobromo analogues.

The methodology is useful for a variety of synthetic purposes. The cycloadditions are not subject to steric hindrance. Thus `diyne' cycloadditions to 2,5-disubstituted furans or pyrroles, followed by elimination of the oxygen or nitrogen bridges, provides an excellent, short route to peri-substituted arenes, as in the following examples:[4,6,7,8]

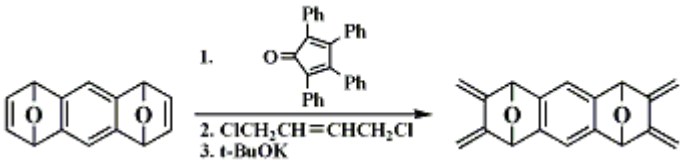


Similar sequences starting with appropriate 1,2,3,4-tetrahaloarenes (1,3-diaryne equivalents) yield hindered phenanthrenes.[9] Cyclopentadienes,[7] fulvenes,[7] isoindoles,[7] anthracenes[10] and other dienes[11] have also been used as `diaryne' traps.

The procedure given here is a modification of the first synthesis of the tetrahydroanthracene diepoxides.[5,7] These compounds have also been prepared from another 1,4-benzadiyne equivalent, namely 1,5-diamino-1,5-dihydrobenzo[1,2-d:4,5-d']bistriazole which, although it has certain advantages,[12] is not as available as 1,2,4,5-tetrabromobenzene.

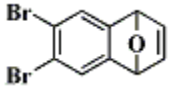


The diepoxide products obtained as described here are excellent bis-dienophiles; hence, they are useful starting materials for further synthesis. They have been used to generate linear acenes,[13,14] iptycenes,[5] and related tetraenes,[15] as exemplified by the following sequence:



They have served as starting points for the synthesis of molecular belts, collars, and strips.[16]

Finally, it should be pointed out that the diaryne reactions of 1,2,4,5-tetrabromobenzene are stepwise. Thus the procedure described here, but using half the amounts of furan and butyllithium, can be used to prepare 6,7-dibromonaphthalene 1,4-endoxide (mp 115-117°C) in 70% yield.[17] This versatile intermediate can then be used as a benzyne precursor, to make unsymmetric adducts;[7,13,17] it also can be used as a dienophile.[15,18]



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

1,2,4,5-Tetrabromobenzene:
Benzene, 1,2,4,5-tetrabromo- (8,9); (636-28-2)

anti-1,4,5,8-Tetrahydroanthracene 1,4:5,8-diepoxide:

1,4:5,8-Diepoxyanthracene,
1,4,5,8-tetrahydro-, (1α,4α,5β,8β)- (11); (87207-46-3)

syn-1,4,5,8-Tetrahydroanthracene 1,4:5,8-diepoxide:
1,4:5,8-Diepoxyanthracene,
1,4,5,8-tetrahydro-, (1α,4α,5α,8α)- (11); (87248-22-4)

Furan (8,9); (110-00-9)

Butyllithium:
Lithium, butyl- (11); (109-72-8)