Organic Syntheses

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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.

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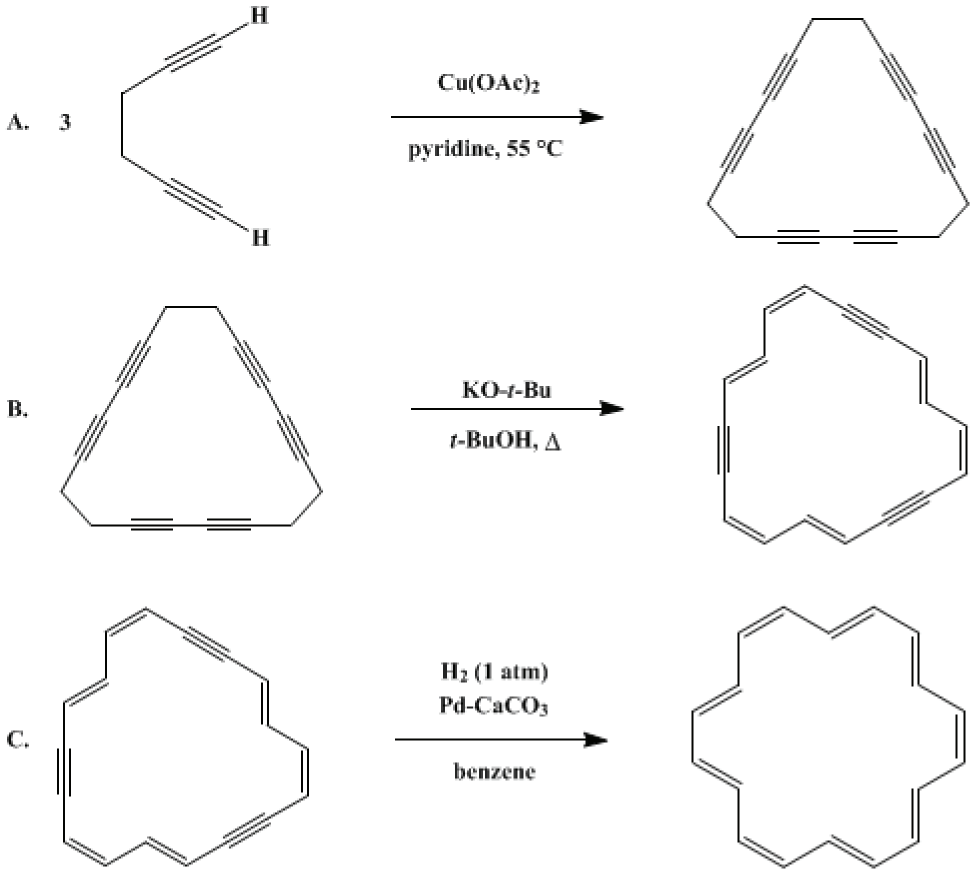
[18]ANNULENE

[1,3,5,7,9,11,13,15,17-Cycloöctadecanonaene]



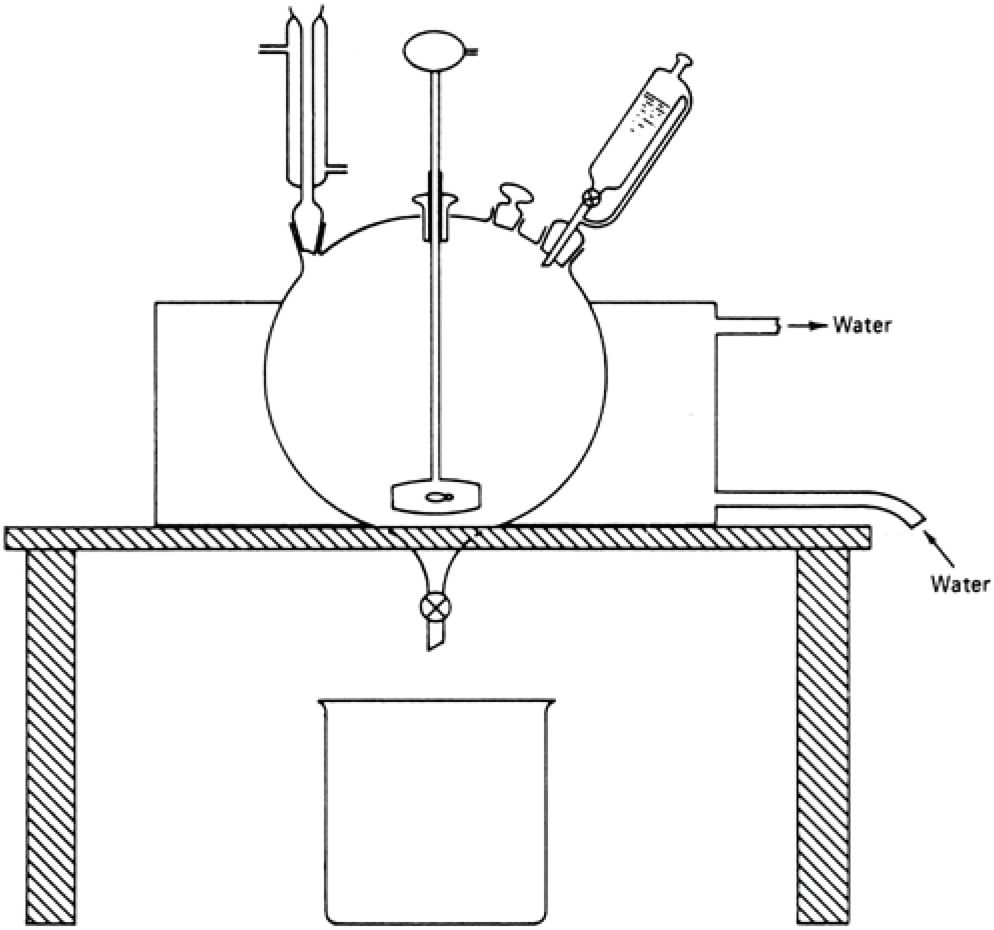
Submitted by K. Stöckel and F. Sondheimer[1].
Checked by R. C. Wheland, R. E. Benson, H. Ona, and S. Masamune.

1. Procedure

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

A. *Hexadehydro*[18]*annulene*. A 12-l., four-necked, round-bottomed flask provided with a stopcock at the bottom (Figure 1) (Note 1) is fitted with a stirrer (Note 2), a reflux condenser, and a 500-ml. pressure-equalizing dropping funnel. The flask is placed in a large metal vessel equipped with a hot–cold water inlet and a drain. The flask is charged with 600 g. (3.00 moles) of copper(II) acetate monohydrate (Note 3) and 3.8 l. of pyridine (Note 4). Stirring is begun and warm water is added to the metal vessel to heat the contents of the flask to 55 ± 1°, and the mixture is slowly stirred at this temperature for 1 hour. With vigorous stirring (approximately 600 r.p.m., (Note 4)), a solution of 50 g. (0.64 mole) of 1,5-hexadiyne (Note 5) in 400 ml. of pyridine (Note 6) is added over 30 minutes to the 55°, green suspension. The mixture is stirred vigorously at this temperature for an additional 2 hours before the warm water in the metal vessel is allowed to drain and is replaced with a mixture of ice and water. When the contents of the flask have cooled, the mixture is drawn off through the stopcock at the bottom of the flask and filtered through a 25-cm. Büchner funnel (Filtrate A). The green residue is transferred to a 5-l. beaker and 2.5 l. of 1:1 (v/v) benzene–diethyl ether is added. The mixture is stirred well, avoiding emulsion formation, and filtered (Filtrate B). The residue is similarly extracted with 2.5 l. of 1:1 (v/v) benzene–ether and filtered (Filtrate C). Each filtrate is kept separate.

Figure 1.



Filtrate A is concentrated to approximately 200 ml. (Note 7) and added to Filtrate C. The resulting mixture is well agitated and filtered through a 25-cm. Büchner funnel. The residue is extracted twice in a similar manner with 500 ml. of 1:1 (v/v) benzene–ether. All the filtrates are now combined in the original 12-l. reaction vessel (Note 8) and washed successively with two 500-ml. portions of water, two 500-ml. portions of cold (0°), 2 *N* hydrochloric acid, and three 500 ml portions of water. The organic layer is dried for 2 hours over *ca.* 110 g. of magnesium sulfate (Note 9), filtered, and evaporated to dryness (Note 7), yielding approximately 16 g. of crude product.

B. *Tridehydro*[18]*annulene*. The dark brown residue from Part A and 800 ml. of benzene (Note 10) are added to a 2-l., round-bottomed flask fitted with a reflux condenser and a calcium chloride drying tube. The solid dissolves on heating to reflux, then the solution is allowed to cool briefly. The condenser is removed, and 800 ml. of a saturated solution of potassium *tert*-butoxide in *tert*-butyl alcohol (Note 11) and (Note 12) is rapidly added (Note 13). After the resulting solution is heated to reflux for 30 minutes, the hot mixture is transferred to the original 12-l. reaction vessel (Note 14), which contains approximately 2 l. of ice, and 1.5 l. of ether is added. The resulting mixture is stirred well then allowed to stand for a few minutes. The incompletely separated phases, in which is suspended a large amount of black solid, are filtered through a 25-cm. Büchner funnel. Whenever the filtration becomes slow, the black material on the filter paper is washed with ether, and the paper is replaced. The organic layer of the filtrate is separated, washed three times with 500-ml. portions of water, dried for 2 hours over *ca.* 100 g. of anhydrous magnesium sulfate (Note 9), filtered, and evaporated to dryness (Note 7) and (Note 15). The red-brown viscous residue is dissolved in 60 ml. of benzene (Note 10) and chromatographed on alumina.

One liter of 95:5 (v/v) pentane–ether (Note 16) is poured into a closed chromatography column (100 × 4.5 cm.), the bottom of which is protected by a small plug of cotton wool. One kilogram of alumina (Note 17) is added in portions, with slow rotation by hand. The stopcock is opened, and the level of the supernatant liquid is allowed to fall to the top of the alumina. The benzene solution is now added with a long pipette and is allowed to seep in. The column is developed first with 1 l. of 95:5 (v/v) pentane–ether in order to wash out the benzene, then with 80:20 (v/v) pentane–ether. Two bands are observable on the column. The faster moving, light brown band consists of tridehydro[18]annulene (Note 18) and the slower moving, dark brown band consists of tetradehydro[24]annulene. When the first band is approximately 15 cm. from the bottom of the column, after approximately 4–6 l. of solvent have been eluted, 150-ml. fractions are collected, and the electronic spectrum of each fraction is determined. As soon as the maxima at 385 and 400 mm. characteristic of tridehydro[18]annulene appear (Note 19), the fractions are combined ("mixed fractions") until the first band is approximately 1 cm. from the bottom of the column. Essentially "pure" tridehydro[18]annulene (Note 18) is now eluted, and this material is collected until the second band is approximately 5 cm. from the bottom of the column. Smaller fractions (150 ml. each) are now collected again; the electronic spectrum of each fraction is determined, and those still showing maxima at 385 and 400 nm. are combined with the previously mentioned "mixed fractions." If required, the tetradehydro[24]annulene suitable for conversion to [24]annulene[2] can then be eluted with pentane–ether (70:30 to 50:50).

The electronic spectrum of the fractions containing the "pure" tridehydro[18]annulene exhibits the strongest absorption maximum (in benzene) at 342 nm. (ε 155,000)[3] and the spectroscopic yield, based on the molar extinction coefficient, is 1.17 g. (2.40% from 1,5-hexadiyne). The yield of tridehydro[18]annulene in the "mixed fractions," based on the 342 nm. maximum, is 0.27 g. (0.55%). The tridehydro[18]annulene is best stored in solution in the refrigerator.

C. [18]*Annulene*. In a 300-ml., conical flask fitted with a side arm (with a closed stopcock) and a 3.5-cm. Teflon®-coated magnetic stirring bar is placed 1 g. of a 10% palladium-on-calcium carbonate catalyst (Note 20) and 30 ml. of benzene (Note 10). The flask is attached to an atmospheric pressure hydrogenation apparatus, and the air in the system is replaced by hydrogen by evacuating the flask and refilling with hydrogen three times. The catalyst suspension is stirred until no more gas is absorbed. One-third (390 mg., determined spectroscopically) of the "pure" tridehydro[18]annulene solution described in Part B is evaporated to dryness (Note 7), and the resulting brown crystalline residue is dissolved in 30 ml. of benzene (Note 10). This solution is added to the hydrogenation flask through the side arm without stirring. The mixture is now stirred under a hydrogen atmosphere as rapidly as possible (*ca.* 600 r.p.m.) (Note 21) until 207 ml. (4.9 molar equivalents) of gas (22°, 740 mm.) are absorbed over *ca.* 5 minutes. The mixture is filtered through a sintered glass funnel, and the catalyst is washed with three 20-ml. portions of benzene.

This hydrogenation experiment is repeated twice with the remaining two-thirds of the "pure" tridehydro[18]annulene solution, and the combined filtrates from the three hydrogenations are evaporated to approximately 30 ml. (Note 7). The solution is then transferred with a pipette to a test tube (10 × 3 cm.) and concentrated to approximately 15 ml. at 40° with a stream of nitrogen. The dark green solution is diluted with 20 ml. of ether and cooled in an ice bath for 30 minutes. The resulting red-brown crystals of [18]annulene are collected by filtration on a sintered glass funnel and washed with approximately 3 ml. of cold (−20°) ether. After drying in air for a few minutes this material weighs 114 mg. A second crop weighing 42 mg. is obtained by evaporation of the mother liquors to dryness (Note 7), followed by crystallization from 6 ml. of benzene and 20 ml. of ether. Both crops give a single spot on TLC (Note 22).

The [18]annulene mother liquors contain 181 mg. of unchanged tridehydro[18]annulene, as determined by the electronic spectrum (see Part B). They are combined with the "mixed fractions" described in Part B (containing 270 mg. of tridehydro[18]annulene), and the resulting solution is evaporated to dryness (Note 7). The residue is dissolved in 30 ml. of benzene and stirred with hydrogen and 1.0 g. of a 10% palladium-on-calcium carbonate catalyst (Note 20), as before, until 216 ml. (4.4 molar equivalents) of hydrogen (20°, 740 mm.) are absorbed. The catalyst is removed, and the filtrate is concentrated to approximately 6 ml., as described previously. After the addition of 20 ml. of ether and cooling in an ice bath, 112 mg. of [18]annulene is collected by filtration (Note 23). The purity of the product is confirmed by TLC (Note 22). The total yield of [18]annulene is 268 mg. (0.54% overall from 1,5-hexadiyne, (Note 24).

[18]Annulene is best stored in benzene–ether solution in the refrigerator. The crystals can also be kept for some time in the refrigerator, small crystals being less stable than large ones.[2] Material that has decomposed to some extent may be purified as follows. The substance (300 mg.) is broken up with a spatula and heated with 30 ml. of benzene, and the insoluble material is removed by filtration. The filtrate is poured onto a chromatography column (20 × 1.8 cm.), prepared with 35 g. of alumina (Note 17) and benzene. The column is washed with benzene until the eluate is colorless. Polymeric material is retained at the top of the column. The eluent is concentrated to approximately 6 ml., diluted with 20 ml. of ether, and cooled in an ice–salt bath. The resulting crystals of [18]annulene are collected on a sintered glass funnel, washed with 3 ml. of cold (−20°) ether, and dried in air for a few minutes.

2. Notes

1. The submitters used an ordinary 10-l., three-necked, round-bottomed flask.
2. A stirrer with one 11-cm., Teflon® blade was employed by the checkers. The submitters used a stirrer with two 7.5-cm. paddles, 9 cm. apart.
3. Copper(II) acetate monohydrate A. R. available from Fisons Scientific Apparatus Ltd. (Loughborough, England) was employed by the submitters. The checkers used both Baker Analytical Reagent and Fisher A.C.S. certified copper(II) acetate monohydrate. Small portions were finely ground with a mortar and pestle.
4. Vigorous stirring is important, since the yield of product appears to be reduced if the mixture is not stirred well.[4] The checkers used rates of 530–560 r.p.m.
5. 1,5-Hexadiyne was obtained from Farchan Research Laboratories and was distilled at atmospheric pressure (b.p. 84–85°) before use. It can be prepared as described by Raphael and Sondheimer.[5]
6. The submitters employed pyridine from BDH Chemicals Ltd. (Poole, England) that was dried over solid potassium hydroxide for 24 hours, then distilled under slightly reduced pressure. The checkers used a similarly treated product.
7. All evaporations, unless otherwise stated, were carried out with a rotary evaporator under reduced pressure (water pump) in a water bath kept at about 40°. The checkers' water bath was maintained at 44–50°, and the evaporation required 4–5 hours rather than the 2 hours found by the submitters.
8. The submitters used a 10-l. separatory funnel.
9. Magnesium sulfate ("dried") from BDH Chemicals Ltd. (Poole, England) was used by the submitters. The checkers used anhydrous magnesium sulfate available from Fisher Scientific Company.
10. Benzene A. R. from Fisons Scientific Apparatus Ltd. (Loughborough, England) was employed by the submitters, and Fisher reagent grade benzene was used by the checkers.
11. The solution was obtained from 44 g. of potassium (Fisons Scientific Apparatus Ltd., Loughborough, England, submitters; Fisher Scientific Company, checkers) and 1 l. of *tert*-butyl alcohol (Note 12) by boiling under reflux under nitrogen, in the apparatus described by Vogel,[6] until all the metal had dissolved. The solution is kept well stoppered. If crystals of potassium *tert*-butoxide separate, they are dissolved by gentle heating before use.
12. *tert*-Butyl alcohol from May & Baker Ltd. of Dagenham, England, was dried by refluxing 1 l. of the alcohol with approximately 40 g. of sodium wire until about two-thirds of the metal had dissolved, and recovering the alcohol by distillation (see Note 2 in Reference [4]). The checkers used *tert*-butyl alcohol available from Fisher Scientific Company and recommend conducting this purification on twofold scale.
13. An exothermic reaction was observed at this point. Too rapid addition of the *tert*-butoxide solution to the benzene solution will lead to loss of product by frothing.
14. The submitters used a 10-l. separatory funnel and shook the mixture after addition to the ice and ether.
15. It is important that all volatile solvents are removed, particularly *tert*-butyl alcohol, since its presence will interfere with the subsequent chromatography procedure. The checkers obtained approximately 9.0 g. of crude material.
16. The submitters used "pentane" petroleum spirit (b.p. 25–40°) available from Hopkin & Williams Ltd., Hadwell Heath, England, and anhydrous ether available from May & Baker Ltd., Dagenham, England. Both solvents were distilled over solid potassium hydroxide before use. The checkers

purchased pentane from Phillips Petroleum Company and distilled it over solid potassium hydroxide. Anhydrous ether supplied by Mallinckrodt Chemical Works was used without further purification.

17. Aluminum oxide (neutral, activity grade I) available from M. Woelm, Eschwege, Germany, was deactivated by the addition of 7 ml. of water to 1 kg. of the adsorbent before use.

18. "Tridehydro[18]annulene" here and in the sequel refers to the symmetrical isomer shown in the formula, admixed with smaller quantities of an unsymmetrical isomer and tetradehydro[18]annulene.[7] These can be separated by chromatography on alumina coated with 20% silver nitrate, but this is unnecessary for the synthesis of [18]annulene, since all three substances give this annulene on catalytic hydrogenation.[7]

19. For the full electronic spectra of tridehydro[18]annulene and tetradehydro[24]annulene in isoöctane, see reference [3].

20. The submitters used 10% palladium-on-calcium carbonate available from Fluka AG, Buchs, Switzerland. The checkers prepared the catalyst in a manner similar to that described by Busch and Stöve.[8] To a solution of calcium chloride (5.1 g.) in 60 ml. of water was added 4.8 g. of sodium carbonate. The precipitate was filtered, washed thoroughly with water, and then suspended in 30 ml. of water. To this calcium carbonate suspension was added with stirring a solution of 0.833 g. of palladium chloride in a few drops of 6 *N* hydrochloric acid. The catalyst mixture was then filtered through a sintered glass funnel, and the solid was washed with water until the chloride test (silver nitrate) became negative. After being washed with ethanol and ether, the catalyst was dried under reduced pressure.

21. Vigorous stirring is essential, since the yield of [18]annulene is reduced considerably if the mixture is stirred more slowly.[9]

22. TLC was performed on silica gel GF_{254} plates supplied by E. Merck AG, Darmstadt, Germany, using (92:4:4) pentane–cyclohexane–benzene. The electronic spectra in benzene were essentially identical to those previously reported,[2] and exhibit absorption maxima at 378 (ε 270,000), 414 (ε 8,600), 428 (6,700), and 455 nm. (26,200). ^{1}H NMR spectra of [18]annulene (tetrahydrofuran-d_8, vacuum-sealed) are temperature-dependent and show a singlet at 5.45 p.p.m. at 120° and two multiplets at 9.25 (12*H*) and −2.9 p.p.m. (6*H*) at −60°. The latter two signals merge just above room temperature.[10] The checkers observed the similar temperature dependence of ^{13}C NMR (tetrahydrofuran-d_8, 22.6 MHz) of the [18]annulene. Thus, proton-decoupled spectra show a singlet at 126 p.p.m. at 60° and two singlets at 128 and 121 p.p.m. at −70°. The rapid processes exchanging the inner and outer nuclei (both proton and ^{13}C) in solution are responsible for the above spectral behavior.

23. The submitters reported in their original procedure that some additional amounts of [18]annulene and tridehydro[18]annulene were obtained by chromatography of the mother liquors.

24. The yields described in Parts B and C are the average values of two runs performed by the checkers, and both runs proceeded with virtually identical results at every stage. The submitters obtained a 0.63% overall yield of [18]annulene from 1,5-hexadiyne.

3. Discussion

Only two general methods have been developed for the synthesis of the macrocyclic annulenes.[11] The first of these, developed by Sondheimer and co-workers, involves the oxidative coupling of a suitable terminal diacetylene to a macrocyclic polyacetylene of required ring size, using, typically, copper(II) acetate in pyridine. The cyclic compound is then transformed to a dehydroannulene, usually by prototropic rearrangement effected by potassium *tert*-butoxide. Finally, partial catalytic hydrogenation of the triple bonds to double bonds leads to the annulene.

The presently described procedure for the synthesis of [18]annulene, although the overall yield is low by the standard normally set for *Organic Syntheses*, illustrates the above general route leading to the theoretically important macrocyclic annulenes, and in this way [14]-, [16]-, [18]-, [20]-, [22]-, and [24]annulenes have been prepared in pure crystalline form.

[18]Annulene was the first macrocyclic annulene containing (4*n* + 2) π-electrons to be synthesized. The compound is of considerable interest, since it is the type of annulene that was predicted to be aromatic by Hückel.[12] It proved to be aromatic in practice, as evidenced from the ^{1}H NMR spectrum,[10,13] the X-ray crystallographic analysis,[14] and the fact that electrophilic substitution reactions could be effected.[15]

The method of synthesis is essentially that described by Sondheimer and Wolovsky[3] (preparation of tridehydro[18]annulene) and by Sondheimer, Wolovsky, and Amiel[2] (hydrogenation of tridehydro[18] annulene to [18]annulene). It has been simplified, since [18]annulene is now obtained from tridehydro [18]annulene without chromatography, and the whole procedure involves only one chromatographic separation. [18]Annulene has also been obtained by Figeys and Gelbcke[16] in 0.42% overall yield by a six-step sequence from propargyl alcohol via propargyl aldehyde, *meso*-1,5-hexadiyne-3,4-diol, *meso*-1,5-hexadiyne-3,4-diol ditosylate, *cis*-3-hexene-1,5-diyne, and 1,3,7,9,13,15-hexadehydro [18]annulene.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 251

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

alumina

silica gel

1,3,7,9,13,15-hexadehydro [18]annulene

Hexadehydro[18]annulene

Tridehydro[18]annulene

tetradehydro[24]annulene

palladium-on-calcium carbonate

tetradehydro[18]annulene

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

silver nitrate (7761-88-8)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

calcium carbonate (471-34-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

potassium (7440-09-7)

Copper(II) acetate (142-71-2)

Pentane (109-66-0)

palladium chloride (7647-10-1)

magnesium sulfate (7487-88-9)

aluminum oxide (1344-28-1)

copper(II) acetate monohydrate (6046-93-1)

tert-butyl alcohol (75-65-0)

propargyl aldehyde (624-67-9)

propargyl alcohol (107-19-7)

isooctane (592-27-8)

[18]Annulene,
1,3,5,7,9,11,13,15,17-Cyclooctadecanonaene (2040-73-5)

1,5-hexadiyne (628-16-0)

[24]annulene

potassium tert-butoxide (865-47-4)

tert-butoxide

meso-1,5-hexadiyne-3,4-diol

meso-1,5-hexadiyne-3,4-diol ditosylate

cis-3-hexene-1,5-diyne

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