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CONVENIENT PREPARATION OF DI- AND TRI-ETHYNYLBENZENES BY CLEAVAGE OF 2-HYDROXY-2-METHYLBUT-3-YN-4-YL-BENZENES WITH WATER MISCIBLE REAGENTS

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Abstract: 2-Hydroxy-2-methylbut-3-yn-4-ylbenzenes, readily available from bromobenzenes, are efficiently cleaved by the water-miscible reagents sodium 2-propoxide in 2-propanol, or potassium hydroxide in dioxan, which facilitates isolation of volatile ethynylbenzenes.

The coupling of aryl bromides and iodides with terminal acetylenes catalysed by palladium(II), or Pd(0), phosphine complexes and copper(I) salts in the presence of amines, due to Sonogashira and co-workers,[1] has greatly facilitated the synthesis of a wide range of arylalkynes. Benzenes substituted by two or more ethynyl groups have become increasingly important as monomers for linear[2,3] and cross-linked[3,4] polymers, leading to carbon-based ceramics including glassy carbon,[5] for the synthesis of unusual structures such as fused biphenylenes[6] and, as in our own work, for the formation of carboranes and ethynylarylcarboranes by condensation of all or some of the triple bonds with decaborane derivatives.

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The preparation of ethynylarenes by this route normally employs a protected ethyne reagent (**1**), giving an intermediate (**3**), from which the terminal alkynyl-compound (**4**) can be liberated in a second step:

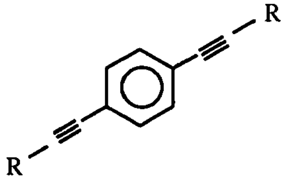
$$\underset{(\mathbf{1})}{HC{\equiv}C{\cdot}R} + \underset{(\mathbf{2})}{ArX} \longrightarrow \underset{(\mathbf{3})}{Ar\text{-}C{\equiv}C{\cdot}R} \longrightarrow \underset{(\mathbf{4})}{Ar\text{-}C{\equiv}C{\cdot}H}$$

Two commercially available protected acetylenes are commonly used: trimethylsilylacetylene (TMSA) (**1**, R = $Si(CH_3)_3$) and 2-methylbut-3-yn-2-ol (**1**, R = $C(CH_3)_2OH$). TMSA has been widely used for ethynyl, and particularly poly-ethynyl-arene synthesis, including that of hexaethynylbenzene,[7] since the silyl group is readily cleaved by hydroxide or fluoride ions. This reagent is, however, expensive and readily lost from the reaction solution owing to its volatility (b.p. 55°C), so that a 10-50% molar excess is frequently used.[8]

Cleavage of the hydroxypropyl group, as acetone, from the methylbutynol intermediate (**3**, R = $C(CH_3)_2OH$) is also base catalysed but requires more vigorous conditions and, since the reaction is reversible, progressive removal of the liberated acetone is advantageous. Various reagents have been used, including sodium hydride, in catalytic amount in toluene at 110°C,[8,9] and alkali hydroxides in boiling toluene,[10] with methanol,[3] or potassium carbonate;[11] nitrobenzene was the solvent for polymeric examples,[12] and ester groups were retained in a solventless process.[13] Phase transfer between benzene and aqueous alkali, in the presence of Pd-Cu catalyst,[14] allows coupling of the liberated ethynyl group with a second aryl halide,[15] but potassium t-butoxide in t-butanol did not fully deprotect the intermediate leading to hexaethynylbenzene.[7]

While these procedures are generally less efficient or convenient than deprotection of TMS intermediates (**3**, R = $Si(CH_3)_3$), the butynol reagent (**1**, R = $C(CH_3)_2OH$) is very much cheaper than TMSA, *e.g.* by a factor of 250,[16] and we here report convenient procedures, applicable to the tens of grams (or larger) scale, for preparation of di- and triethynylbenzenes using the cheaper reagent.

Using $Pd[(C_6H_5)_3P]_2Cl_2$ and CuI, condensation of 1,4-di- and 1,3,5-tribromobenzenes with the butynol reagent (**1**, R = $C(CH_3)_2OH$) in boiling diethylamine gave the intermediate diol[10] (**5**, R = $C(CH_3)_2OH$), 97%, and triol[3] (**6**, R = $C(CH_3)_2OH$), 80%, but as previously reported[14] the *ortho*-isomer (**7**, R = $C(CH_3)_2OH$) needed boiling piperidine (106°C) and several by-products were detected, giving 65% yield of crystalline diol. The required ethynes are stable to alkali, but some are too volatile to be conveniently separated from high-boiling solvents like toluene.[17] We therefore investigated deprotection in water-soluble systems and extraction of the product with low-boiling solvents, ether, pentane or petroleum ether. We tried sodium alkoxides in the corresponding alcohol, and alkali hydroxides in water-soluble oligo-ethers.



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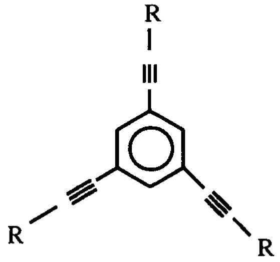

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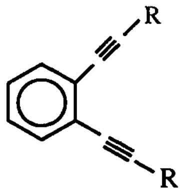
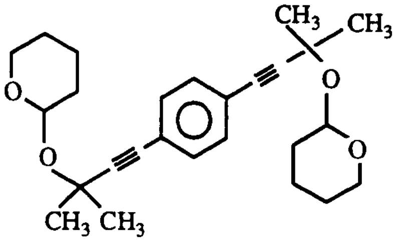


(7)

The *para*-isomer (**5**, R = C(CH$_3$)$_2$OH) gave very little reaction with sodium methoxide in boiling methanol (65°C) but, using a dinitrogen flow to remove liberated acetone, the reagent from sodium and 2-propanol under reflux (*ca.* 85°C) gave almost pure 1,4-diethynylbenzene (**5**, R = H) in 85% yield after vacuum sublimation; the yield and purity were slightly inferior using KOH in dioxan. With a crude sample of the *ortho*-diol (**7**, R = C(CH$_3$)$_2$OH) this reagent gave 1,2-diethynylbenzene in 36% yield for the two steps; we believe this to be the first preparation of this compound by this route.[14]

We obtained 76% of sublimed triyne (**6**, R = H) using sodium 2-propoxide which is similar to Marvel's yield[3] from toluene; sodium or potassium hydroxides in triethyleneglycol dimethyl ether at 80° were almost equally effective.

Since the 1-*ortho*carboranyl group is likely to be more readily displaced as its anion[18] than is alkynyl, we investigated conversion of the triple bonds of the 1,4-diol (**5**, R = C(CH$_3$)OH) into carborane cages *before* cleavage of the hydroxypropyl groups. To protect the hydroxyl groups for this step we prepared the bis-2-tetrahydropyranyl derivative (**8**), as a mixture of diastereomers, from (**5**) and 2,3-dihydropyran. The ^{1}H NMR spectrum shows distinct resonances for the axial and equatorial protons at C6 of the pyran ring at 20°C and two methyl signals, which we attribute to restricted rotation of the tetrahydropyranyloxy groups, rather than to different shifts for the two diastereomers, since the two asymmetric centres (pyran C2) are far apart; the intensities of the signals remain similar after recrystallisation which may be expected to change the proportion of the two isomers. In the event, condensation of the derivative (**8**) with decaborane[19] was not efficient owing, perhaps, to hindrance by the quaternary alkynyl substituents.



(**8**)

In conclusion, we have found that the intermediates readily formed from aryl bromides (or iodides) with 2-methylbut-3-yn-2-ol (1, R = $C(CH_3)_2OH$) are efficiently cleaved at 80-100°C by sodium 2-propoxide in 2-propanol, or by alkali hydroxides in dioxan or other water-miscible oligo-ethers, to give ethynylbenzenes which are easily isolated using water and low-boiling extraction solvents.

EXPERIMENTAL

Materials and General Methods: Di- and tribromobenzenes, 2-methylbut-3-yn-2-ol, bistriphenylphosphine palladium(II) chloride, copper(I) iodide, 2,3-dihydropyran, toluene-4-sulphonic acid monohydrate and amine solvents were commercial materials used without purification. Chromatographic silica gel refers to Merck Kieselgel 60, Art. 9385. Thin layer chromatography (t.l.c.) was conducted on Merck DC-Plastikfolien Art. 5735 eluted with chloroform containing 7% v/v of ethanol for alcohols, or cyclohexane for hydrocarbons. Melting points were observed in capillary tubes using electronic temperature measurement. Solutions were dried over magnesium sulphate before evaporation using a rotary evaporator evacuated by a water-jet pump at the stated bath temperatures.

Ethynylbenzenes were purified, as stated, by sublimation under vacuum below 55°C and/or by recrystallisation.

CAUTION: EXPLOSIONS HAVE BEEN REPORTED WHEN POLYETHYNYLBENZENES WERE HEATED.[8,20]

1,4-Bis(2-hydroxy-2-methyl-4-but-3-ynyl)benzene (5, R = $C(CH_3)_2OH$): 1,4-Dibromobenzene (47.2 g, 0.20 mole) and 2-methylbut-3-yn-2-ol (46.0 cm^3, 0.48 mole) in diethylamine (250 cm^3) were stirred and flushed with dinitrogen for 1.5 h. Bistriphenylphosphinepalladium chloride (561 mg, 0.80 mmole) and copper(I) iodide (161 mg, 0.85 mmole) were added[21] and the mixture was heated under reflux for 16 h. Precipitated diethylammonium bromide was separated after cooling and the solvent was evaporated (bath *ca.* 40°C). The crystalline residue was recrystallised from toluene (*ca.* 400 cm^3) to give light brown sandy crystals of the diol (47.1 g, 97%) m.p. 157-159°C suitable for preparation of 1,4-diethynylbenzene. Further recrystallisation gave an analytical sample m.p. 159-161°C. Lit.[10] 162-163°C (from dichloromethane). Found: C, 79.12; H, 7.43. Calc. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49%.

The bistetrahydropyranyl derivative (8) was prepared by adding toluene-4-sulphonic acid monohydrate (25 mg) to a solution of the diol (**5**) (2.18 g) and 2,3-dihydropyran (3.5 cm^3) in dioxan (20 cm^3). Although reaction was almost complete (by t.l.c.) within 1 h. the mixture was allowed to stand overnight, diluted with ether (50 cm^3), washed with dilute (2%) potassium hydrogen carbonate solution (100 cm^3) and water (2 x 100 cm^3), dried and evaporated. The solid residue (3.54 g) was recrystallised from acetonitrile (*ca.* 12 cm^3) to give colourless crystals of *the derivative* (2.72 g, 73%) m.p. 108-110°C. Found: C, 76.05; H, 8.35; $C_{26}H_{34}O_4$ requires: C, 76.15; H, 8.52%. δ ^{1}H ($CDCl_3$, 200 MHz, 20°C): 1.50-1.90 (m, pyran H3, 4 and 5) and superimposed 1.580, 1.622 (s, s, CH_3; total relative intensity 6H); 3.518 (quintet [ddd, J 11.5, 5.7, 5.7 Hz] r.i. 1H, pyran 6H axial); 3.980 (ddd, J 11.5, 5.5, 4.1 Hz, r.i. 1H, pyran 6H equatorial); 5.120 (dd, J 5.4, 2.7 Hz, r.i. 1H pyran H2); 7.339 (s, r.i. 2H, benzene H).

1,2-Bis(2-hydroxy-2-methyl-4-but-3-ynyl)benzene (7, R = $C(CH_3)OH$): treatment of 1,2-dibromobenzene as in the previous preparation, but using piperidine at reflux in place of diethylamine, gave an oil (*ca.* 100%) containing several minor impurities including the monosubstituted intermediate (by t.l.c.). Crystalline material was obtained by washing an ether solution of the oil successively with dilute (2M) hydrochloric acid and water, drying, filtration through a short column of chromatographic silica gel and trituration of the residue after evaporation of the solvent (bath 40°C) with a mixture of pentane and cyclohexane (1:1, v:v). Recrystallisation from cyclohexane using charcoal gave pale yellow glistening plates m.p. 73-76°C, lit.[14] 73° (from di-isopropyl ether). Found: C, 79.54; H, 7.67; Calc. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49.

1,3,5-Tris(2-hydroxy-2-methyl-4-but-3-ynyl)benzene (6, R = C(CH₃)OH): 1,3,5-Tribromobenzene (3.20 g, 0.01 mole) and 2-methylbut-3-yn-2-ol (5.80 cm^3, 0.06 mole) were condensed in diethylamine (22 cm^3) using the same conditions and catalyst to alkyne molar ratio (*ca.* 1:600) as in the first preparation; reaction was essentially complete in 5.5 h. and only minor amounts of by-products were detected (by t.l.c.). The oily product crystallised on trituration and washing with cyclohexane to give a brown powder (3.48 g) which was recrystallised by adding water (15 cm^3) to its solution in ethanol (13.5 cm^3) at 60°C, and then from xylene (*ca.* 30 cm^3) to give well-formed but discoloured blades (2.60 g, 80%) m.p. 170-172°C. Further recrystallisation from aqueous ethanol using charcoal gave a colourless sample of the same m.p., lit.[3] 170-171°C. Found: C, 77.90; H, 7.64; Calc. for $C_{21}H_{24}O_3$: C, 77.73; H, 7.46%.

1,4-Diethylnylbenzene (5, R = H): (a) Using sodium- 2-propoxide: The 1,4-bisbutyndiol (8.10 g) was added to the warm solution obtained by dissolving sodium (330 mg) in 2-propanol (80 cm^3) and the mixture was heated under reflux with a slow stream of dinitrogen passing through the flask and out of the condenser. After 4.5 h. the cooled solution was diluted with ether, washed with water (500 cm^3, 2 x 125 cm^3), dried and evaporated (bath *ca.* 15°C). The light brown crusty residue (4.22 g) was sublimed at *ca.* 0.5 mm, bath 40-45°C, to give the diyne as a dry white powder (3.58 g, 85%) m.p. *ca.* 90-94°C, pure enough for most purposes. Found: C, 94.66; H, 5.10. Calc. for $C_{10}H_6$: C, 95.24; H, 4.76%. Recrystallisation from aqueous (90%) ethanoic acid gave transparent plates m.p. 94-96°, lit.[22] 95°.

(b) Using potassium hydroxide in dioxan: Potassium hydroxide (*ca.* 1.0 g) was quickly powdered in air and added to a solution of the diol (6.58 g) in dioxan (60 cm^3) and the mixture, which becomes black and deposits a sludgy solid, was heated under reflux as in the previous preparation. Isolation as before, using

pentane, and sublimation at 45°C gave the diyne (1.96 g, 57%) m.p. 90-94°C; a further crop (0.78 g, total 80%) m.p. *ca.* 84-89° was obtained by raising the sublimation temperature to 60°C.

1,2-Diethylnylbenzene (7, R = H): The crude diol obtained as above from 1,2-dibromobenzene (11.8 g) was dissolved in chloroform (200 cm^3), filtered through a column of chromatographic silica gel (30 g), the solvent was evaporated (bath 40°C) and the residue was redissolved in dioxan (150 cm^3). Powdered potassium hydroxide (*ca.* 2.4 g) was added and the mixture was heated, and then extracted with pentane, as in the previous preparation to give a brown oil (5.40 g). Two vacuum transfers at 0.05 mm gave a nearly pure (by i.r.) pale yellow sample of the diyne (2.20 g, 36%) Found: C. 94.74; H, 5.04. Calc. for $C_{10}H_6$: C, 95.24; H, 4.76%.

1,3,5-Triethynylbenzene (6, R = H): The triol (5.0 g) was deprotected as in method (a) for 1,4-diethynylbenzene, above, using sodium (350 mg) in 2-propanol (75 cm^3) to give, after sublimation at 40-45°, 0.01 mm, the triyne (1.75 g, 76%) m.p. 94-98°C. Found: C, 95.43; H, 4.16. Calc. for $C_{12}H_6$: C, 95.97; H, 4.03%. One recrystallisation from ethanol gave off-white needles m.p. 104-105°C, lit.[3,23] 104-105°C, 105-107°C.

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