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A mild and efficient method for the synthesis of mixed adducts of 1,4-bis-benzyne

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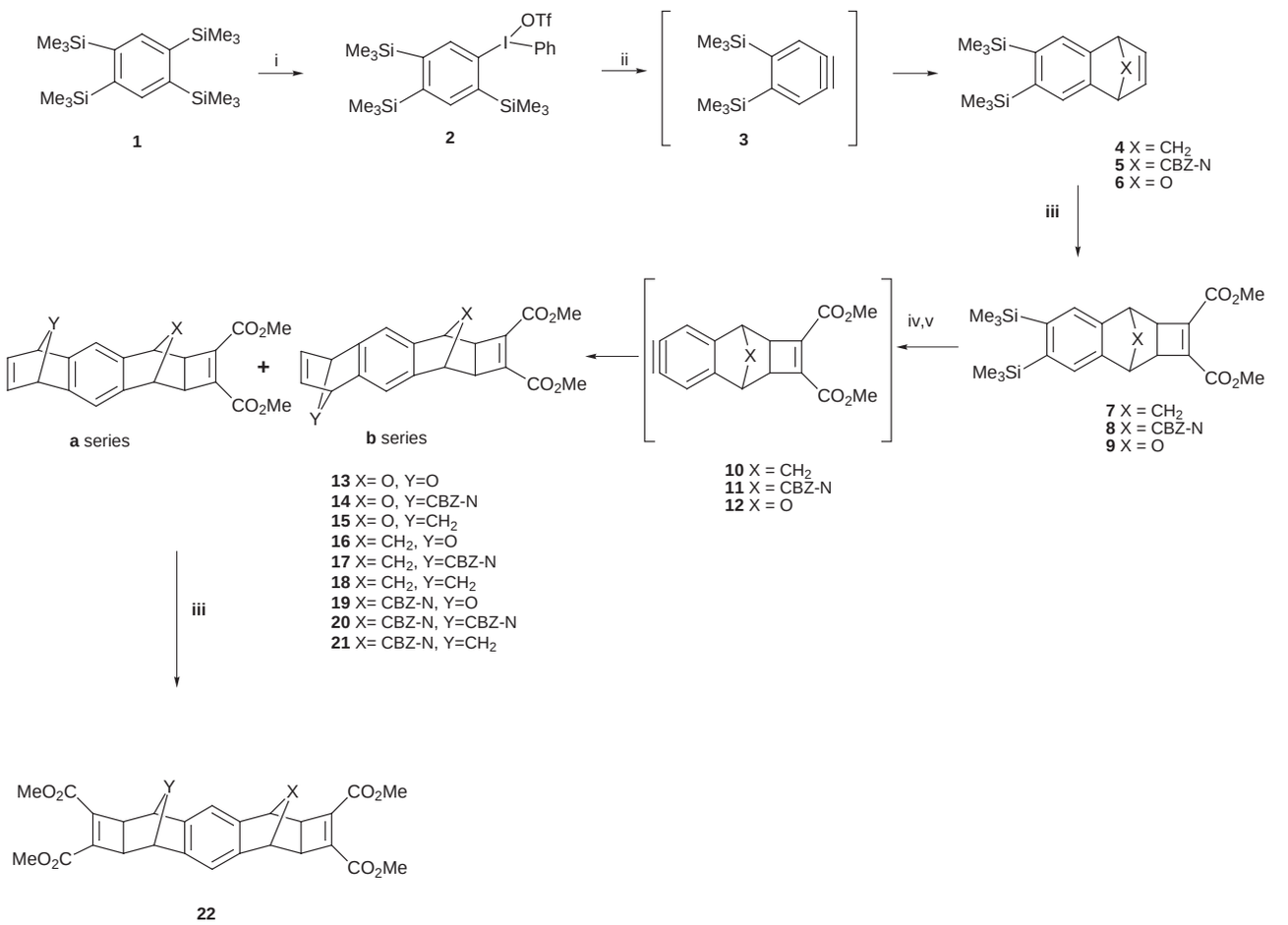
Unsymmetrical adducts of 1,4-bis-benzyne† have been prepared by the addition of dienes to monobenzynes generated sequentially from 1,2,4,5-tetrakis(trimethylsilyl)benzene.

1,4-Bis-benzyne is a versatile intermediate for the construction of polycyclic supramolecular assemblies[1] and we have been particularly interested in the application of its *syn*-adducts with heterodienes to the construction of cavity shaped molecules.[2] Although numerous routes to adducts of 1,4-bis-benzyne with a single diene have been described, we could find no methods which provided controlled access to adducts from two different dienes, under mild and neutral conditions.[3,4] Recently Kitamura and co-workers reported that phenyl[*o*-(trimethylsilyl)phenyl]-iodonium triflate reacts with tetrabutylammonium fluoride (TBAF) to generate benzyne under conditions which enable it to be trapped with dienes in extremely high yield.[5] In this communication we report an extension of this strategy and describe improved reaction conditions which facilitate the sequential generation of the reactive sites of 1,4-bis-benzyne from the readily available 1,2,4,5-tetrakis(trimethylsilyl)benzene.[6]

The reaction (Scheme 1) of 1,2,4,5-tetrakis(trimethylsilyl)-benzene **1** with iodobenzene diacetate ($PhI(OAc)_2$, 1.5 equiv.) and trifluoromethanesulfonic acid (TfOH, 3 equiv.) in the presence of diisopropylamine (Pr^i_2NH, 2 equiv.) afforded phenyl-[2,4,5-tris(trimethylsilyl)phenyl] iodonium triflate **2** which could be isolated and characterised. The presence, in the reaction mixture, of two equivalents of diisopropylamine was found to be crucial as it suppressed the otherwise major side reaction of ipso-protonation of one of the trimethylsilyl groups.

In practice however it was not necessary to isolate product **2** and 4,5-bis(trimethylsilyl)benzyne **3** could be generated, in solution, using TBAF (1.7 equiv.) and trapped *in situ* with an appropriate diene (cyclopentadiene, *N*-CBZ-pyrrole or furan)



Scheme 1 *Reagents and conditions*: i, $PhI(OAc)_2$ (1.5 equiv.), TfOH (3 equiv.), dry DCM, 0 °C, room temp., 1 h, 0 °C; **1** (1 equiv.), dry DCM, Pr^i_2NH (2 equiv.), 0 °C; ii, Pr^i_2NH (1 equiv.), C_4H_4X (1.1 equiv.), n-$Bu_4NF{\cdot}3H_2O$ (1.7 equiv.) in THF; iii, DMAD (1.1 equiv.), $RuH_2CO(PPh_3)_3$ (10%), C_6H_6, reflux, 20 h; iv, $PhI(OAc)_2$ (1.5 equiv.), TfOH (3 equiv.), dry DCM, 0 °C, room temp., 1 h, 0 °C; v, **7** or **8** or **9** (1 equiv.), Pr^i_2NH (1 equiv.), 0 °C, 10 min; Pr^i_2NH (2 equiv.); C_4H_4X (1.1 equiv.), n-$Bu_4NF{\cdot}3H_2O$ (1.7 equiv.) in THF.

in a one pot reaction. Under these conditions the addition of one further equivalent of Pr^i_2NH, immediately prior to the addition of the diene and TBAF, was found to be advantageous and the adducts **4**–**6** were obtained in close to quantitative yield.‡§ Even though our specific target molecules **22** were destined to have identical cyclobutene terminals, subsequent chromatographic separations made it desirable to modify the ring strained double bond of the initial adduct before undertaking a second aryne addition. This was achieved by a Ru-catalysed [2 + 2] cycloaddition of dimethyl acetylenedicarboxylate (DMAD),[7] to **4**, **5** and **6** thereby producing the new aryne precursors **7**, **8** and **9** in high yield.§ Generating the second benzyne from these compounds proved somewhat more challenging and required strict control of both the reaction conditions and the sequence in which reagents were added. Optimum yields§ were obtained when the bis(trimethylsilyl) adducts **7**–**9** were reacted with $PhI(OAc)_2$ (1.5 equiv.) and TfOH (3 equiv.) in the presence of Pr^i_2NH (1 equiv.) until the starting material had disappeared. Two further equivalents of Pr^i_2NH were then added followed by 1.1 equivalents of the appropriate benzyne acceptor (furan, cyclopentadiene or *N*-CBZ-pyrrole) and TBAF (1.7 equiv.) predissolved in dry THF. These conditions afforded the adducts **13**–**21**, as a mixture of *syn*- and *anti*-isomers, in yields ranging from 69 to 98% (Scheme 1).¶ The stereoisomers of **13**, **19** and **20** were separated using centrifugal radial chromatography on silica with a 1:10 ethyl acetate:hexane mixture as eluent and the *syn*-isomers subjected to a second Ru(0) catalysed addition with DMAD. The stereochemistry of the bis-oxa-adduct **13b** followed from a previous crystal structure[8] of the simple bis-furan adducts of 1,4-bis-benzyne. In addition we unambiguously identified the *anti*-isomer **20b** by single crystallographic analysis and note that as with the bis-oxa-analogues **13a** and **b**, the least polar adduct possessed *anti*-stereochemistry.

In summary, we have developed new conditions for the preparation of adducts of 1,4-bis-benzyne under mild conditions and these clearly have a wider application in the field of cycloaddition chemistry.

Experimental

The following examples are typical experimental techniques.

Monoadduct 5

A solution of $PhI(OAc)_2$ (1.50 equiv.; 13.93 mmol; 4.49 g) in CH_2Cl_2 (45 ml) was cooled to 0 °C and treated dropwise with TfOH (3 equiv.; 27.87 mmol; 4.18 g; 2.47 ml). After 1 h at room temperature the reaction was again cooled to 0 °C (ice bath) and treated dropwise with a cold (0 °C) solution of the arene **1** (1 equiv.; 9.29 mmol; 3.40 g) and diisopropylamine (2 equiv.; 18.58 mmol; 1.88 g; 2.60 ml) in CH_2Cl_2 (30 ml). After 10 minutes, additional diisopropylamine (1 equiv.; 9.29 mmol; 0.94 g; 1.30 ml) was added and the solution allowed to warm to room temperature. *N*-Benzyloxycarbonylpyrrole (1.1 equiv.; 10.22 mmol; 2.05 g) was added, followed by a solution of $nBu_4NF{\cdot}3H_2O$ (1.7 equiv.; 15.79 mmol; 4.98 g) in THF (20 ml). After a further 10 min, H_2O (100 ml) was added to the mixture which was subsequently extracted three times with CH_2Cl_2 (100 ml). The organic phase was dried over $MgSO_4$, filtered, evaporated and the residue purified by column chromatography (silica/1:4 EtOAc–hexane), to afford the adduct **5** (3.63 g; 93%) as a colourless solid, mp 110–112 °C; δ_H(300 MHz, $CDCl_3$)‖ 0.43 + 0.44 (18H, 2s), 5.08 (2H, br s), 5.60 (2H, br s), 6.96 + 7.01 (2H, br d), 7.19–7.36 (5H, m), 7.58 (2H, br s); δ_C(75 MHz, $CDCl_3$) 2.06, 66.16, 66.99, 126.89 + 127.26, 127.53, 127.86, 128.29, 136.187, 142.26 + 143.39, 143.29, 147.27, 154.94; *m*/*z* (ES): MH^+: 422, MNa^+: 444, MK^+: 460.

Formation of cyclobutene 8

A solution of the adduct **5** (7.12 mmol; 3.00 g), $RuH_2CO(PPh_3)_3$ (300 mg) and dimethyl acetylenedicarboxylate (1.1 equiv.; 7.83 mmol; 1.11 g; 0.96 ml) in benzene (40 ml) was heated at 80 °C for 20 h. The solvent was removed, the residue redissolved in CH_2Cl_2 and filtered through a pad of Celite to remove the ruthenium catalyst. The residue, recovered from the filtrate, was purified by column chromatography (silica/1:2 EtOAc–hexane) to afford the cyclobutene **8** (3.48 g; 87%), mp 140–142 °C; δ_H(300 MHz, $CDCl_3$) 0.26 + 0.31 (18H, 2s), 2.87 + 2.91 (2H, 2s), 3.66 + 3.88 (6H, 2s), 4.95 (1H, d, *J* 4 Hz), 5.05 (1H, d, *J* 4 Hz), 5.21 + 5.26 (2H, 2s), 7.25–7.33 (5H, m), 7.62 + 7.67 (2H, 2s); δ_C(75 MHz, $CDCl_3$) 2.03, 46.07 + 46.14, 51.92 + 52.12, 59.18 + 59.46, 66.83, 126.56 + 126.92, 127.58, 127.82, 128.30, 136.14, 142.11, 143.23 + 144.10, 145.45 + 145.56, 155.23, 160.46 + 160.63; *m*/*z* (ES) MH^+: 564.

syn and *anti* adducts 20

A solution of $PhI(OAc)_2$ (1.50 equiv.; 7.99 mmol; 2.57 g) in CH_2Cl_2 (45 ml) was cooled to 0 °C and treated dropwise with TfOH (3 equiv.; 15.98 mmol; 2.40 g; 1.41 ml). After 1 h at room temperature the reaction was again cooled to 0 °C (ice bath) and treated dropwise with a cold (0 °C) solution of the adduct **8** (1 equiv.; 5.32 mmol; 3.00 g) and diisopropylamine (1 equiv.; 5.32 mmol; 0.54 g; 0.75 ml) in CH_2Cl_2 (25 ml). After 10 minutes, additional diisopropylamine (2 equiv.; 10.65 mmol; 1.08 g; 1.49 ml) was added and the solution allowed to warm to room temperature. *N*-Benzyloxycarbonylpyrrole (1.1 equiv.; 5.86 mmol; 1.18 g) was added, followed by a solution of $nBu_4NF{\cdot}3H_2O$ (1.3 equiv.; 6.92 mmol; 2.18 g) in THF (20 ml). After being allowed to react for a further 10 min, H_2O (100 ml) was added and the resulting mixture extracted three times with CH_2Cl_2 (100 ml). The organic phase was dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (silica/1:1 EtOAc–hexane) afforded the *syn*- and *anti*-adducts **20** (2.77 g; 84%) as a 1:1 mixture. Further separation of these two isomers was achieved by slow centrifugal radial chromatography (silica/1:6 EtOAc–hexane).

anti-**20**: mp: 157–159 °C; δ_H(300 MHz, $CDCl_3$) 2.77 + 2.81 (2H, 2s), 3.66 + 3.87 (6H, 2s), 4.89–5.16 (6H, m), 5.59 (2H, s), 6.97 + 7.02 (2H, br d), 7.26–7.31 (14H, m); δ_C(75 MHz, $CDCl_3$) 45.85 + 45.94, 52.00 + 52.24, 58.92 + 59.29, 66.25 + 66.94, 67.31 + 68.01, 127.65 + 127.85, 127.90 + 128.12, 128.24, 128.35 + 128.43, 128.58, 136.08 + 136.11, 140.55, 143.33 + 144.23, 147.84, 155.00 + 155.24, 160.49 + 160.69; *m*/*z* (ES) MNa^+: 641; MK^+: 657.

syn-**20**: mp: 93–95 °C; δ_H(300 MHz, $CDCl_3$) 2.79 + 2.83 (2H, 2s), 3.65 + 3.87 (6H, 2s), 4.94–5.16 (6H, m), 5.55 (2H, s), 6.99 (2H, br d), 7.21–7.36 (14H, m); δ_C(75 MHz, $CDCl_3$) 45.78 + 46.31, 52.12 + 52.49, 59.39 + 59.78, 66.24 + 66.97, 67.26 + 67.97, 127.46 + 127.63, 127.78 + 128.07, 128.22 + 128.36, 128.70, 136.08, 140.35, 143.44 + 144.35, 155.08, 160.52 + 160.70; *m*/*z* (ES) MNa^+: 641; MK^+: 657.

syn-Adduct 22 (X = Y = *N*-CBZ)

This product was prepared in 82% from the *syn*-adduct of **20** using the method described above for the catalysed addition of DMAD, mp 170–172 °C; δ_H(300 MHz, $CDCl_3$) 2.82 + 2.86 (4H, 2s), 3.63 + 3.85 (12H, 2s), 4.89 (2H, d, *J* 12.1 Hz), 5.01 (2H, d, *J* 12.1 Hz), 5.14 + 5.20 (4H, 2s), 7.21–7.34 (12H, m); δ_C(75 MHz, $CDCl_3$) 45.95, 52.02 + 52.26, 58.99 + 59.35, 67.06, 113.34 + 114.03, 113.76, 127.73, 127.77, 127.95, 135.98, 143.97, 155.22, 160.50 + 160.63; *m*/*z* (ES) MNa^+: 783, MK^+: 799.

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Notes and references

† '1,4-Bis-benzyne' refers to the unisolated benzene derivative with two triple bonds at the 1 and 4 position.

‡ All new compounds gave satisfactory spectroscopic and analytical data.

§ Compounds (yield %); **4** (94), **5** (93), **6** (96), **7** (97), **8** (87), **9** (94), **13** (96), **14** (77), **15** (76), **16** (90), **17** (69), **18** (74), **19** (77), **20** (84), **21** (78).
¶ The *syn*- and *anti*-isomers of all other compounds except **14** were separated by reversed-phase HPLC using a C18 column with a mixture of water (60%) and acetonitrile (40%) as eluent.
‖ Both ^{1}H and ^{13}C NMR spectra of all CBZ protected compounds show duplication of some but not all resonances due to hindered rotation about the C–N bond. In such cases related pairs of resonances are linked with a + sign.

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