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New persubstituted 1,3,5-trisethynyl benzenes via Sonogashira coupling

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Abstract—Starting from 1,3,5-trifluoro-2,4,6-triiodobenzene, selective Sonogashira coupling gave trisalkynylbenzenes, which can be further functionalized making use of the reactive fluorine substituents on the benzene core. Along the way, a conceivably trivial deprotection step unexpectedly led to a pentasubstituted benzene derivative the structure of which was revealed by X-ray crystallography.

Over the past few years, the synthesis of highly substituted trisethynylbenzenes has gained increasing attention due to their use in the construction of carbon-rich scaffolds and fullerene fragments,[1] molecular materials[2] and supramolecular systems.[3]

The key step to obtain alternatingly substituted benzenes is the sequential functionalization of suitable benzene precursors. Metal catalyzed [2+2+2] cyclo-trimerization of unsymmetrically substituted alkynes usually gives statistical mixtures of regioisomers instead of the desired symmetric compound as the major product.[4]

Three generally different strategies have been usefully applied: benzene-1,3,5-tricarbaldehyde **1** has been used as a key precursor in the synthesis of alternatingly persubstituted hexaethynylbenzenes **1**[5] employing Corey's formyl–ethynyl conversion.[6] Recently, an elegant strategy was reported by Tobe and co-workers.[7] The stepwise functionalization of 1,3,5-trichloro-2,4,6-triiodobenzene gave alternatingly substituted hexaethynylbenzene derivatives. This synthetic approach made use of the different reactivities of halogen atoms in palladium-catalyzed cross-coupling reactions, that is, Sonogashira and Negishi coupling yielding compounds of type **2**. Nuckols et al. obtained molecular materials for liquid crystal applications by subjecting pre-functionalized benzenes to Stille coupling reactions,[8] conceptually in a similar manner to that reported earlier affording compounds of type **3** (Fig. 1).[3]

In the context of supramolecular architecture and molecular materials, we were interested in developing a versatile synthetic strategy for the preparation of persubstituted 1,3,5-trisalkynylbenzenes, which permits the introduction of different functionalities on the acetylenic periphery as well as on the central benzene core. Periodination of 1,3,5-trifluorobenzene **4** with periodic acid using a known method cleanly gave the suitably differentiated precursor **5**, the 'missing link' in the mixed perhalobenzene series, in good yield (Scheme 1).[9] Standard Sonogashira coupling of **5** with trimethylsilylacetylene or phenylethylene yielded the 1,3,5-trisalkynyl compounds **6** and **7** in 71% and 69%, respectively.[10] As expected, the fluorine substituents were not affected in the coupling reactions.[11] It can be easily imagined that

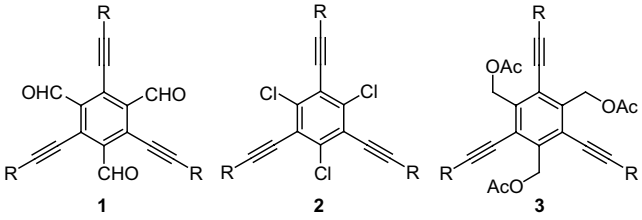

Figure 1.

Keywords: Sonogashira coupling; Molecular scaffolding; Crowded benzenes; Acetylene compounds.
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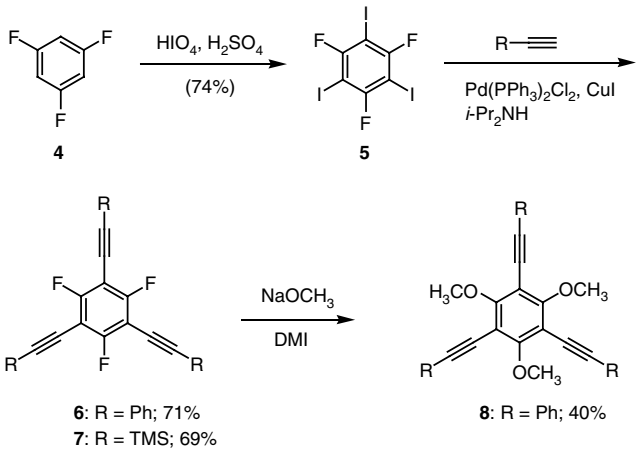


Scheme 1.

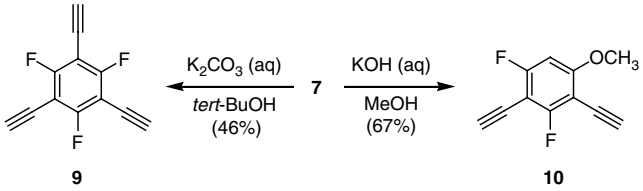
other peripheral functionalities can be introduced as their alkynyl derivatives in a similar fashion.

Compound **6** with its strongly electron withdrawing fluorine substituents can be converted into the trimethoxy derivative **8** by applying conventional aromatic substitution chemistry in 1,3-dimethyl-2-imidazolidinone (DMI) as a solvent. In this type of reaction, fluorine is an ideal leaving group, hence, it serves as a masking unit allowing for further diversification of the trisalkynylbenzene.

Nevertheless, it would appear advantageous to attach different fragments to the free acetylenic functions of the benzene core after removal of the protecting groups. Therefore, we sought to obtain trisethynylbenzene **9** upon standard TMS deprotection of **7** using an aqueous base (K_2CO_3 or KOH) in methanol solution.[12]

To our surprise, when the deprotection was attempted with potassium hydroxide as base in MeOH, compound **10** bearing two unprotected ethynyl functions and a methoxy substituent was obtained as the only isolable product in 67% yield (Scheme 2). The same result was obtained by using the milder base K_2CO_3 in MeOH, albeit in a lower isolated yield (27%).

Unequivocal proof of the structure of **10** was obtained by X-ray crystallography (Fig. 2).[†]



Scheme 2.

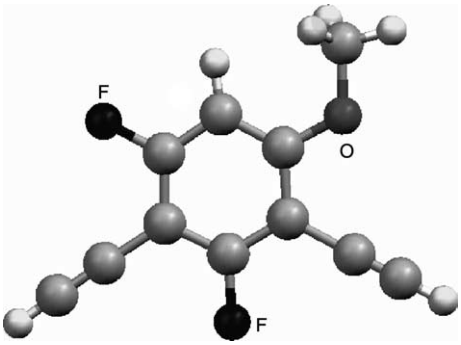


Figure 2. X-ray structure for 1,3-bis(ethynyl)-2,4-difluoro-6-methoxybenzene (**10**), ball and stick representation. All bond lengths and torsion angles are in the same range as expected for comparable aromatic or acetylenic systems, respectively.

Although the substitution of a fluoride by a methoxy group is not fully unexpected, the loss of the alkynyl fragment appears to be unprecedented. Substitution of the acetylide anion by a hydrogen could be formally interpreted as the nucleophilic attack of a hydride transferred from the methoxide anion (with methanol being oxidized yielding formaldehyde), which replaces the acetylide anion as a leaving group. Although in the context of nucleophilic acetylenic substitutions, the generation of the $RC{\equiv}C^-$ anion has been observed as a result of the nucleophile attacking the supposed leaving group itself,[13] we do not know of any comparable example in aromatic substitution chemistry.

Finally, smooth deprotection of **7** was achieved by employing potassium carbonate in *tert*-butanol. The generation of hydride is neither possible in this solvent nor does the alkoxide react as a nucleophile.

The trisethynyl benzene **9** can be considered as a model compound potentially susceptible to further coupling reactions at the terminal alkyne functions and possessing an electronically tunable benzene core by varying the substituents in the 2-, 4- and 6-positions.

In summary, we have developed a versatile synthetic route for the synthesis of persubstituted, C_3-symmetric 1,3,5-triethynylbenzenes, complementary to existing methods. This strategy allows tailoring of both the acetylenic periphery as well as the benzene core in a modular fashion. The curious finding manifested by the pentasubstituted benzene derivative **10** reiterates the importance of a cautious choice of appropriate conditions and reagents in conceivably trivial transformations.

[†] Crystal data for **10**: Colorless prisms were grown from methanol, triclinic, P-1 (no 2), $Z = 2$ in a cell of dimensions: $a = 7.1442(3)$, $b = 7.7004(4)$, $c = 9.6192(5)$ Å, $\alpha = 68.565(3)°$, $\beta = 68.651(3)°$, $\gamma = 74.527(3)°$, $V = 453.29(4)$ Å^3, $Z = 1$, $\rho_{calc} = 1.408$ Mg/m^3, $\mu = 1.012$ mm^{-1}, $F(000) = 196$. A total of 2695 reflections were measured, 1489 unique ($R_{int} = 0.0251$). F^2 refinement, $R_1 = 0.0740$, $wR_2 = 0.1465$.

CCDC 225013 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

Characterization of compounds

1,3,5-Trifluoro-2,4,6-tris(trimethylsilanylethynyl)benzene (**7**). Mp 78–80 °C; ^{1}H NMR (200 MHz): $\delta = 0.26$ (s, 27H, CH_3); ^{13}C NMR (75 MHz): $\delta = 162.96$ (d, $J_{CF} =$ 263.1 Hz, Ar–F), 88.55 (Ar), 88.02, 85.87 (C≡*C*), 0.53 (*C*H$_3$); EI$^+$-MS m/z 420 (43, [M^+]). HRMS found: 420.1391; calculated for $C_{21}H_{27}Si_3$: 420.1373. $R_f = 0.47$ (Hex).

1,3,5-Triethynyl-2,4,6-trifluorobenzene (**9**). Mp 94–96 °C (subl.); ^{1}H NMR (200 MHz): $\delta = 3.53$ (s, 3H, C≡*CH*); ^{13}C NMR (75 MHz): $\delta = 163.92$ (dm, $J_{CF} = 256.8$ Hz, Ar–F), 98.13 (m, Ar), 88.43, 87.18 (C≡*C*); EI$^+$-MS m/z 204 (100, [M^+]). HRMS found: 204.0189; calculated for $C_{12}H_3F_3$: 204.0187. $R_f = 0.67$ (20:1 Hex–Et$_2$O).

1,3-Bis(ethynyl)-2,4-difluoro-6-methoxybenzene (**10**). Mp 97–98 °C (subl.); ^{1}H NMR (200 MHz): $\delta = 6.48$ (d, $J_{HF} = 11.0$ Hz, 1H, Ar*H*), 3.91 (s, 3H, OCH_3), 3.49 (s, 1H, C≡C*H*), 3.43 (s, 1H, C≡C*H*); ^{13}C NMR (75 MHz): $\delta = 165.28$ (dd, $J_{CF} = 257.8$, 10.5 Hz, Ar–F), 164.13 (dd, $J_{CF} = 256.8$, 8.4 Hz, Ar–F), 162.20 (Ar*C*–OCH$_3$), 95.57–95.18 (m, Ar*C*–H), 86.51–86.15 (m, Ar*C*–C≡C), 71.59, 69.83 (C≡*C*); EI$^+$-MS m/z 192 (100, [M^+]). HRMS found: 192.0388; calculated for $C_{11}H_6OF_2$: 192.0387. $R_f = 0.29$ (20:1 Hex–Et$_2$O).

Acknowledgements

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