Short communication

Synthesis of Some Acetylene-tethered Chiral and Achiral Dialdehydes

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Abstract

A convenient synthesis of some acetylene-tethered chiral and achiral dialdehydes using Sonagashira-Hagihara coupling has been accomplished. Dibromobenzenes and enantiopure dibromobinaphthol were functionalized to provide the acetylene-tethered dialdehydes in moderate to good yields.

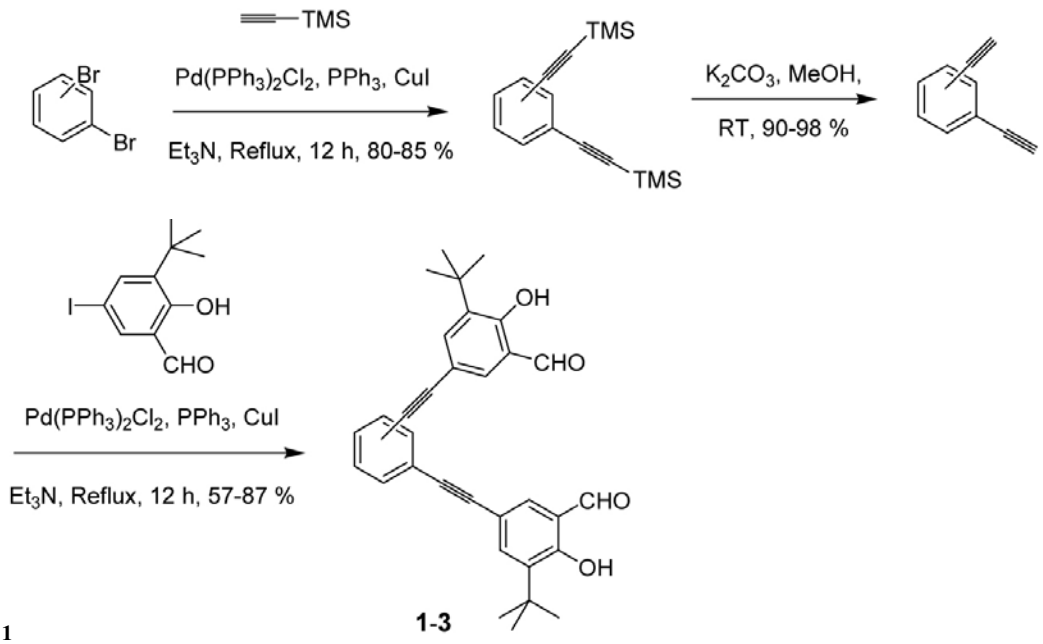
Keywords: Acetylene, dialdehydes, Sonagashira-Hagihara coupling, binaphthyl.

1. Introduction

The design and study of new macrocyclic species is one of the most important and interesting areas in the field of supramolecular chemistry.[1] In particular, chiral macrocyclic compounds have been studied extensively for their applications in molecular recognition, host-guest chemistry, supramolecular structures, material chemistry and catalysis.[2] Schiff base chemistry has been successfully applied to construct both chiral and achiral macrocycles with different ring sizes.[3] The conformation and the structure of dialdehyde component of these macrocycles play a significant role in the yield and the nature of macrocycle formed in the reaction. Dialdehydes with spacers between the aldehyde moieties often generate interesting macrocyclic structures. The spacers used in this regard range from one atom linker to multi-atomic chains.[4] Chiral and achiral [n+n] macrocycles with different order of macrocyclisation can thus be constructed by a proper choice of these spacers. Acetylene spacers are particularly attractive as they are used to construct shape-persistent and rigid macrocycles.[5] Achiral salophen and salen based macrocycles containing acetylene spacers were synthesized in good yields and their photophysical properties were investigated.[6] As an extension of our earlier work on the synthesis of chiral macrocyclic Schiff bases,[7] we report the synthesis of new rigid achiral (**1**–**3**) and chiral (**4**) dialdehydes containing acetylene spacers.

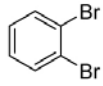
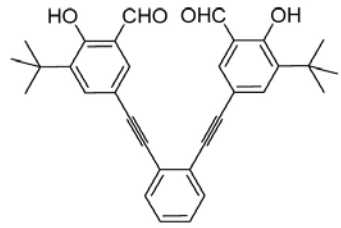
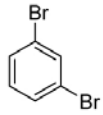
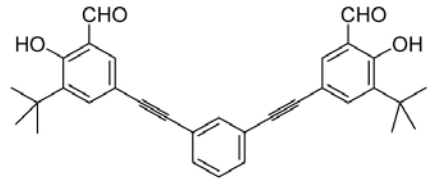
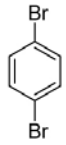
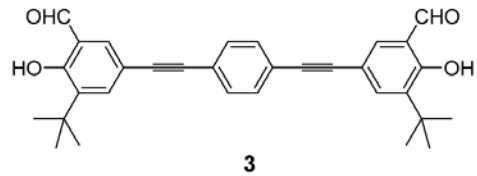
2. Results and Discussion

The incorporation of acetylene groups as spacers improves the rigidity of the dialdehydes thereby facilitating the synthesis of macrocycles with larger central cavities in good yields. A series of dialdehydes containing acetylene spacers varying in their respective positions at their core moiety were synthesized starting from disubstituted benzenes. *tert*-Butyl groups were incorporated into the structure of these dialdehydes to provide a steric environment during the construction of macrocyclic ligands and also improve their solubility in organic solvents. Scheme 1 shows the general pathway for the synthesis of acetylene based achiral dialdehydes **1**–**3**. Dibromo-substituted benzene cores were used for the construction of these dialdehydes. Palladium-catalyzed Sonogashira cross-coupling[8] of starting dibromobenzenes with trimethylsilylacetylene in refluxing triethylamine afforded the corresponding bis(2-(trimethylsilyl)ethynyl)benzenes in high yields. Deprotection of TMS group under basic condition using potassium carbonate in methanol gave diacetylene-



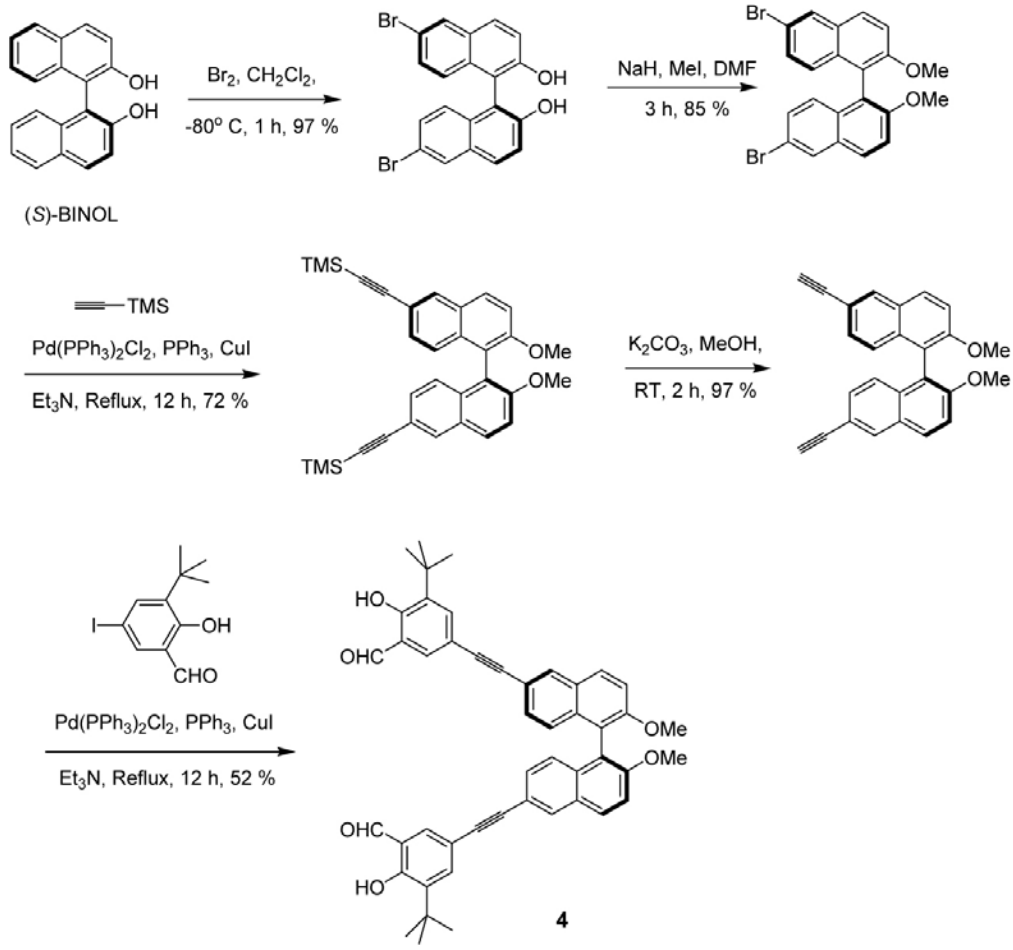
Scheme 1

Table 1: Structures and yields of acetylene-tethered achiral dialdehydes **1–3**

Dibromobenzene	Dialdehyde	Yield (%)
	 **1**	57
	 **2**	82
	 **3**	87

benzenes in good yields. Pd-catalysed Sonogashira coupling of these acetylene derivatives with 3-*tert*-butyl-2-hydroxy-5-iodobenzaldehyde resulted in acetylene-tethered dialdehydes **1**–**3** in moderate to good yields depending upon the position of the two acetylene groups.

Dialdehydes **2** and **3** with two acetylene groups either *meta* or *para* to each other were formed in good yields in comparison to dialdehyde **1** with two acetylene moieties *ortho* to each other. The yields of various acetylene-spaced dialdehydes are given in Table 1. Synthesis of so-



Scheme 2

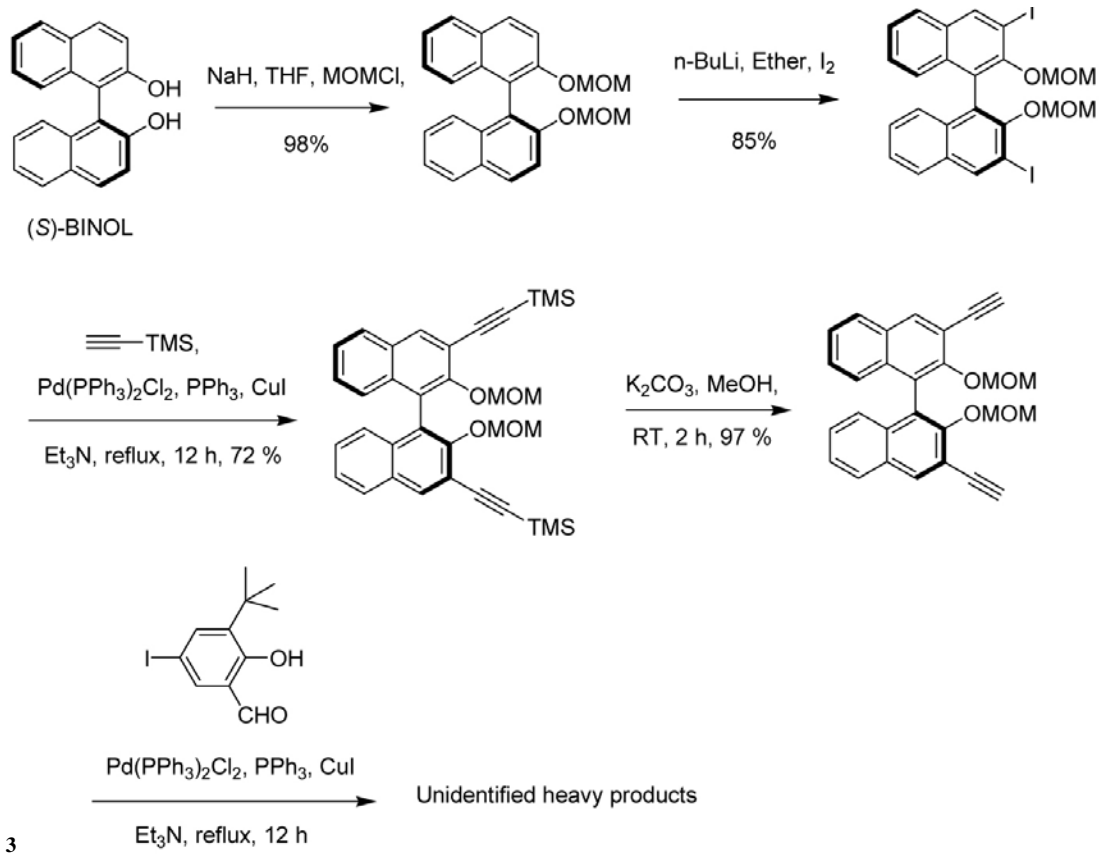
me acetylene-tethered chiral dialdehydes was attempted in a similar manner starting from chiral (*R*)- and (*S*)-BINOL according to Scheme 2.[9] Bromination of (*S*)-BINOL at –78 °C afforded (*S*)-6,6'-dibromo-1,1'-binaphthyl-2,2'-diol in almost quantitative yield. Methylation of brominated BINOL was then achieved using NaH and methyl iodide in 85% yield.

Pd-catalysed Sonogashira-Hagihara coupling of these dibromides with trimethylsilylacetylene followed by deprotection of trimethylsilyl groups under basic condition at reflux afforded the (*S*)-6,6'-diethynyl-2,2'-dimethoxy-1,1'-binaphthyl in good yield. A second Sonogashira-Hagihara coupling of diacetylene derivative with 3-*tert*-butyl-2-hydroxy-5-iodobenzaldehyde gave the chiral dialdehyde (*S*)-**4** in 52% yield. The enantiomeric excess of the compound (*S*)-**4** was determined by Chiralcel OD HPLC column. The *ee* of the compound (*S*)-**4** was found to be >99%. Furthermore, it was also compared with the product obtained in a similar way from racemic BINOL. The other enantiomer of the dialdehyde, i.e. (*R*)-**4**, was obtained in a similar fashion starting from (*R*)-BINOL. In an attempt to synthesize a variant of the dialdehyde **4** and incorporate the acetylene moieties at 3,3´-positions of BINOL, a similar strategy was followed starting from enantiopure (*S*)-BINOL as depicted in Scheme 3.[10] (*S*)-BINOL was protected as methoxymethyl (MOM) ether using methoxymethyl chloride and NaH. Directed *ortho*-lithiation of the MOM-protected (*S*)-BINOL followed by quenching with I_2 resulted in introduction of iodo groups at 3,3´-position in 85% yield.

Pd-catalysed Sonogashira-Hagihara coupling of this diiodide with trimethylacetylene followed by deprotection of trimethylsilyl groups under basic condition afforded the corresponding diacetylene derivative in good yield. Unexpectedly, second Sonogashira-Hagihara coupling of this diacetylene derivative with 3-*tert*-butyl-2-hydroxy-5-iodobenzaldehyde did not afford the expected dialdehyde, instead, the reaction resulted in unidentified heavy products together with an unexpected cyclic product.

3. Conclusions

A facile method for the synthesis of acetylene-tethered dialdehydes is described. Achiral dialdehydes **1**–**3** with acetylene tethers at different positions were synthesi-



Scheme 3

zed in good to moderate yields. On the other hand, BINOL based chiral dialdehydes with acetylene spacers are strongly dependent on the position of acetylene groups. Acetylene moieties *ortho* to ether group underwent polymerization whereas acetylene moieties at other positions (5,5´-positions of BINOL) afforded the expected dialdehyde **4** in good yield with excellent enantiopurity.

4. Experimental Section

4. 1. General Procedures

^{1}H NMR spectra were recorded at 400 MHz on Bruker AVANCE 400 spectrometer and ^{13}C NMR spectra were recorded at 100 MHz on the same instrument using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT/IR 100 spectrometer. Melting points were recorded on Buchi melting point apparatus Model B-545 and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 series II CHN analyser. Mass spectra were recorded on ESI MS mass spectrometer. Optical rotations were measured by a Rudolph Autopol V polarimeter. All the reactions were monitored by thin layer chromatography (TLC). TLC was performed on F_{254}, 0.25 mm silica gel plates (Merck). Plates were eluted with appropriate solvent systems, and then stained with either alkali $KMnO_4$ or ceric ammonium molybdate solutions prepared in the laboratory. The developed plates were first analysed under UV at 254 nm then stained with appropriate reagent. Column chromatography was performed using silica gel with particle size 100–200 mesh.

4. 2. General experimental procedure for the synthesis of acetylene spacered dialdehydes under Sonogashira-Hagihara cross-coupling reaction

Under a nitrogen atmosphere, 3-*tert*-butyl-2-hydroxy-5-iodobenzaldehyde (0.760 g, 2.5 mmol), *trans*-dichlorobis(triphenylphosphine)palladium(II) (0.056 g, 0.08 mmol), copper(I) iodide (0.030 g, 0.16 mmol) and triphenylphosphine (0.042 g, 0.16 mmol) were dissolved in dry triethylamine (*ca*. 20 mL) and stirred at room temperature for 15 min. Freshly prepared bis(ethynylbenzene) (or (*S*)-6,6'-diethynyl-2,2'-dimethoxy-1,1'-binaphthyl) (1 mmol) dissolved in 10 mL of dry triethylamine was added dropwise at room temperature for over a period of 10 min and then the reaction mixture stirred at reflux for further 6 h. Triethylamine was removed under reduced pressure and the reaction mixture was diluted with EtOAc. The organic layer washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude compound. Purification of the crude compound by column chromatography over silica gel using 10% EtOAc in hexane as an eluent afforded pure acetyle-

ne spacered bis(hydroxyaldehyde) **1**–**4** as a white solid in 57–87% yield.

5,5-(1,2-Phenylenebis(ethyne-2,1-diyl))bis(3-*tert*-butyl-2-hydroxybenzaldehyde) **(1)**: Yield 57%; mp. 115–116 °C; IR (KBr): 3216, 2965, 1655, 1620, 1552, 1495, 1224, 1125, 986, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.91 (s, 2H), 9.78 (s, 2H), 7.65–7.64 (d, *J* = 1.6 Hz, 2H), 7.60–7.59 (d, *J* = 1.6 Hz, 2H), 7.55–7.53 (dd, *J* = 5.3 Hz, 2H), 7.32–7.30 (dd, *J* = 5.3 Hz, 2H), 1.54 (s, 18H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 196.5, 161.4, 139.1, 137.2, 135.0, 131.7, 128.1, 125.6, 120.5, 114.3, 92.5, 87.2, 34.9, 29.0; ESI-MS: *m/z* 479 ($[M+H]^+$); *Anal* calcd. for $C_{32}H_{30}O_4$: C, 80.31; H, 6.32%. Found: C, 80.21; H, 6.30%.

5,5-(1,3-Phenylenebis(ethyne-2,1-diyl))bis(3-*tert*-butyl-2-hydroxybenzaldehyde) **(2)**[11]: Yield 82%; IR (KBr): 3179, 2873, 2348, 1912, 1648, 1605, 1554, 1436, 1270, 967, 795 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.95 (s, 2H), 9.87 (s, 2H), 7.71 (s, 1H), 7.68–7.67 (d, *J* = 2.1 Hz, 2H), 7.62–7.61 (d, *J* = 2.1 Hz, 2H), 7.51–7.50 (d, *J* = 1.6 Hz, 1H), 7.49–7.48 (d, *J* = 1.6 Hz, 1H), 7.36–7.33 (t, *J* = 6.4 Hz, 1H), 1.44 (s, 18H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 196.6, 161.4, 139.0, 137.0, 135.2, 134.4, 131.1, 128.6, 123.6, 120.5, 114.0, 89.0, 87.5, 35.0, 29.1; ESI-MS: *m/z* 479 ($[M+H]^+$).

5,5-(1,4-Phenylenebis(ethyne-2,1-diyl))bis(3-*tert*-butyl-2-hydroxybenzaldehyde) **(3)**[11]: Yield 87%; IR (KBr): 3277, 2962, 1659, 1625, 1556, 1494, 1262, 1125, 860, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.86 (s, 2H), 9.79 (s, 2H), 7.60–7.59 (d, *J* = 2.1 Hz, 2H), 7.54–7.53 (d, *J* = 2.1 Hz, 2H), 7.43 (s, 4H), 1.36 (s, 18H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 196.6, 161.4, 139.1, 137.0, 135.1, 131.5, 123.0, 120.6, 114.1, 90.3, 88.1, 35.0, 29.1; ESI-MS: *m/z* 479 ($[M+H]^+$).

(*S*)-5,5-(2,2-Dimethoxy-1,1-binaphthyl-6,6-diyl) bis(ethyne-2,1-diyl)bis(3-*tert*-butyl-2-hydroxybenzaldehyde) **(4)**: Yield 52%; $[\alpha]_D^{29}$ = 221 (*c* 1.1, CH_2Cl_2); *ee* > 99%; mp. 160–162 °C (dec); IR (KBr): 3442, 3250, 2925, 2853, 1658, 1622, 1402, 1232, 1041, 972, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.83 (s, 2H), 9.79 (s, 2H), 8.01 (s, 2H), 7.90–7.88 (d, *J* = 9.2 Hz, 2H), 7.61–7.60 (d, *J* = 2.1 Hz, 2H), 7.55–7.54 (d, *J* = 2.1 Hz, 2H), 7.42–7.39 (d, *J* = 9.2 Hz, 2H), 7.25–7.22 (dd, J_1 = 8.8 Hz, J_2 = 1.2 Hz, 2H), 7.01–6.99 (d, *J* = 8.8 Hz, 2H), 3.71 (s, 6H), 1.36 (s, 18H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 195.7, 160.1, 154.7, 137.9, 136.1, 134.1, 132.4, 130.6, 128.5, 127.8, 127.7, 124.3, 119.5, 118.1, 117.0, 113.6, 113.5, 87.9, 87.1, 55.7, 34.0, 28.1; ESI-MS: *m/z* 715 ($[M+H]^+$); *Anal* calcd. for $C_{48}H_{42}O_6$: C, 80.65; H, 5.92%. Found: C, 80.54; H, 5.94%.

5. References

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Povzetek

S pomočjo Sonogashira-Hagihara reakcije je bila dosežena prikladna sinteza nekaterih kiralnih in akiralnih dialdehidov z acetilenskimi mostički. Na ta način z zmernimi do dobrimi izkoristki poteka funkcionalizacija dibromobenzenov in enantiočistih dibromobinaftolov do dialdehidov povezanih z acetilenskimi mostički.