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NATURALLY OCCURRING 5-[(2-THIENYL)ETHYNYL]THIOPHENE-2- CARBALDEHYDE THROUGH A SHORT SYNTHESIS OF DIARYLACETYLENES.

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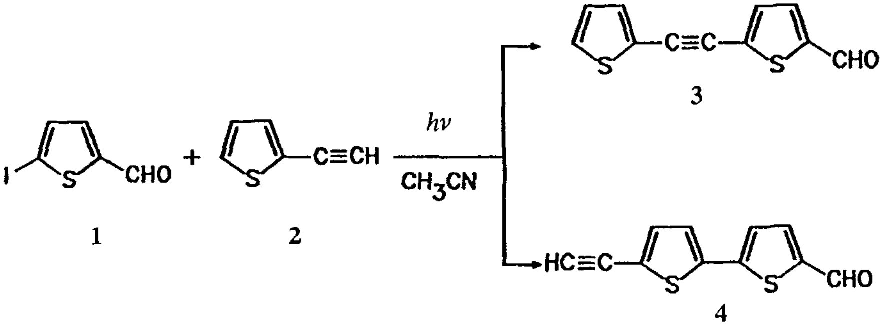
Abstract: title compound and related diarylacetylenes were synthesized *via* a one-pot procedure starting from aryliodide and trimethylsilylacetylene.

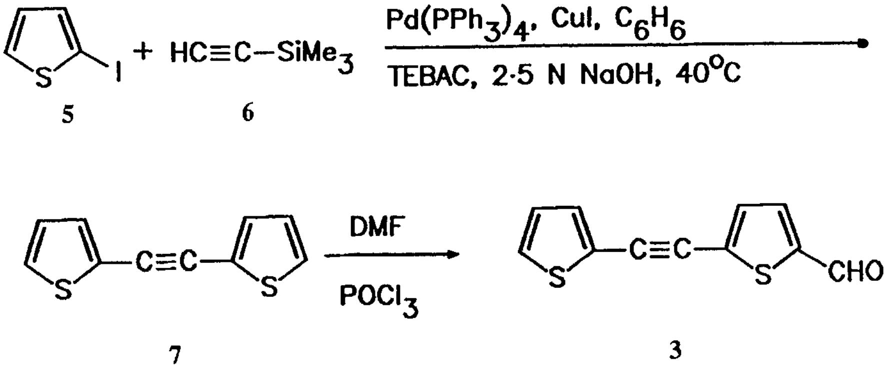
Recently we have reported that the irradiation of 5-iodo-2-thiophenecarbaldehyde (1) in acetonitrile in the presence of ethynylthiophene (2) gave a mixture of bithienylacetylenes 3 and 4.[1] By using diluted solutions of both 1 and



2 the formation of 3 can be optimized. 5-[(2-Thienyl)ethynyl]thiophene-2-carbaldehyde 3 is a naturally occurring bithienylacetylene isolated in *Berkheya armata*, *Berkheya herbacea*, *Berkheya purpurea*, and *Berkheya rigida*.[2] Unfortunately our photochemical approach required very diluted solutions (10^{-3} M) and then allowed us to obtain very low quantity of 3 for biological tests. In order to obtain larger quantity of this compound we have studied its chemical synthesis. Compound 3 can be obtained starting from 2,2'-bithienylacetylene *via* a Vilsmeier-Haack reaction.[3] This compound can be obtained using several methodologies. Bohlmann reported that a Wittig reaction between 2-thiophenecarbaldehyde and triphenylphosphine-2-thienyl-methylide gave 1,2-bi-(2-thienyl)ethylene (73% yield). Subsequently, bromination of the alkene and debromination gave 2,2'-bithienyl-acetylene.[3] Unfortunately Bohlmann did not give the yields of these two steps. Alternatively 2-trimethylsilylethynylthiophene can be coupled with 2-iodothiophene in the presence of Pd(0) as catalyst.[4] 2-Thienyl-trimethylsilylacetylene can be synthesized starting from trimethylsilylacetylene and 2-halothiophene derivatives through reaction of trimethylsilylacetylene with EtMgBr and subsequent reaction of the Grignard reagent with 2-iodothiophene in the presence of $Pd(PPh_3)_4$,[5] or through reaction of the same acetylene with 2-bromothiophene in the presence of $Pd(PPh_3)_4$, triphenylphosphine, CuI and pyperidine.[6] Furthermore we have to note that probably 2,2'-bithienylacetylene could be obtained directly from 2-iodothiophene *via* reaction with 2-methyl-3-butyn-2-ol in the presence of $Pd(PPh_3)_4$, CuI, TEBAC under phase transfer conditions: unfortunately the authors did not prepare this compound.[7] Nevertheless the reported yields were not very high.

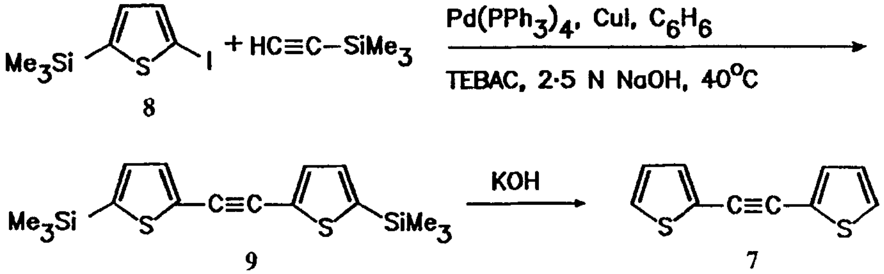
In this paper, we want to report a new approach to the synthesis of 5-[(2-thienyl)ethynyl]thiophene-2-carbaldehyde 3 and related compounds. We have found that treatment of 2-iodothiophene (5) with trimethylsilylacetylene (6) in the presence of both $Pd(PPh_3)_4$ and CuI and in phase transfer conditions at 40°C directly gave 2,2'-bithienylacetylene (7) in 91% yield.

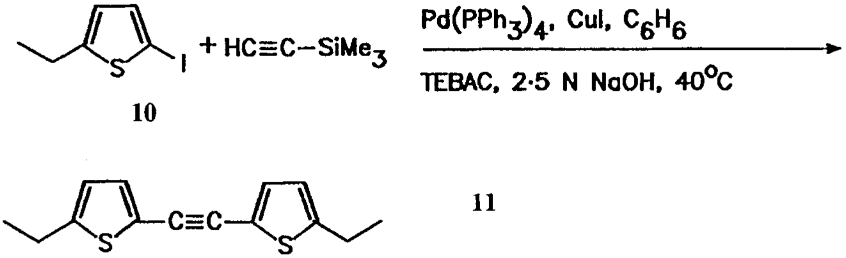
Compound 7 can be converted into 3 through a Vilsmeier-Haack reaction in 53% yield. Probably the basic aqueous medium when the reaction is carried

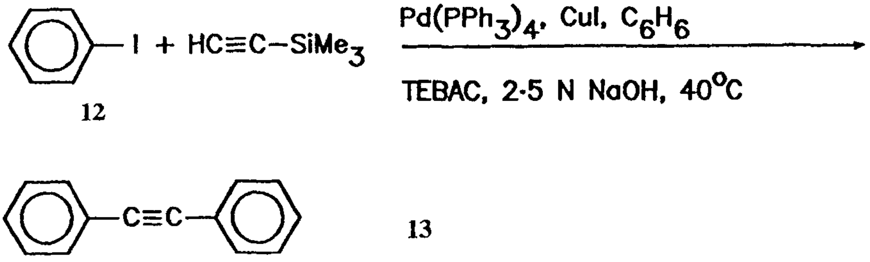


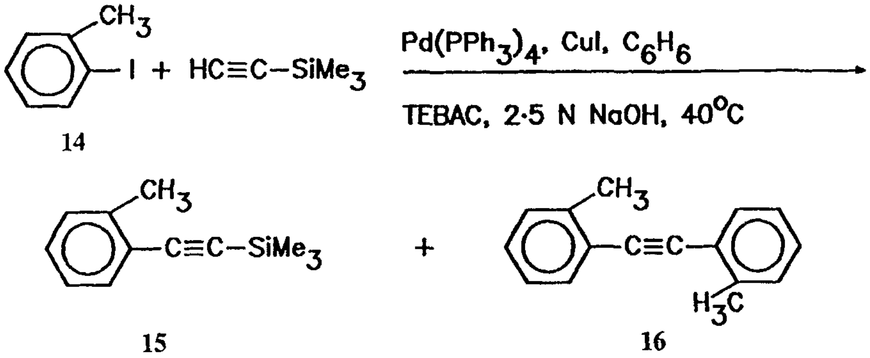
out causes the removal of the silyl group to give an alkyne which reacts with 2-iodothiophene to afford 7.

The same result can be obtained using 2-iodo-5-trimethylsilylthiophene (8) as starting material. Subsequent desilylation of the product gave 7 in 92%









yield. Using 2-iodo-5-ethylthiophene (10) the product 11 can be isolated in 75% yield. On the contrary the reaction did not work using 2-bromothiophene as starting material.

The observed reactivity can be used in the synthesis of phenyl substituted derivatives. While iodobenzene gave 13 in 76% yield, *o*-methyl-iodobenzene furnished only a mixture of 15 and 16 in 46 and 40% yields respectively. Probably the reaction suffers of the steric hindrance of the substrate.

In conclusion the above described conversions represent a useful method for the synthesis in high yields of symmetric substituted acetylenes.

Experimental

Starting Materials

All the compounds are commercialy available. Only5-ethyl-2-iodothiophene and 5-trimethylsilyl-2-iodothiophene were prepared. 5-Ethyl-2-iodothiophene was synthesized from 2-ethylthiophene (Fluka) by reaction with iodine and HgO. 5-Trimethylsilyl-2-iodothiophene was prepared *via* reaction of 2-iodothiophene with LDA and trimethychlorosilane (73% yield). ^{1}H NMR ($CDCl_3$) δ: 7.24 (d, 1 H, J = 3.5 Hz), 6.90 (d, 1 H, J = 3.5 Hz), 0.28 (s, 9 H); MS (*m/z*): 282 (M^+), 267 (100%), 185.

Synthesis of diarylacetylenes - General Procedure

5 Mmoles of haloaryl derivatives was dissolved in benzene (20 ml) under argon. Trimethylsilylacetylene (10 mmoles), $Pd(PPh_3)_4$ (600 mg), CuI (160 mg), TEBAC (120 mg), and deareated 2.5 N NaOH (20 ml) were added. The mixture was stirred at 40°C for 48 h. Saturated NH_4Cl was added, and the mixture was stirred for 0.5 h. Then the mixture was extracted with Et_2O. The neutral extracts were dried (Na_2SO_4). Removal of the solvent yielded a crude product that was chromatographed on SiO_2. Elution with *n*-hexane gave the pure product.

2,2'-bithienylacetylene 7

^{1}H NMR ($CDCl_3$) δ: 7.27 (m, 2 H), 7.00 (m, 1 H); IR ($CHCl_3$) ν_{max}: 2140 cm^{-1}; MS (*m/z*): 192 (10), 191 (13), 190 (100), 189 (8), 158 (9), 146 (9), 145 (13), 114 (9), 95 (7), 93 (5), 87 (4), 69 (8), 58 (4%).

5-Trimethylsilyl-2-[(5-trimethylsilyl-2-thienyl)-ethynyl]- thiophene 9

^{1}H NMR ($CDCl_3$) δ: 7.27 (d, 1 H, J = 3.6 Hz), 7.09 (d, 1 H, J = 3.6 Hz), 0.30 (s, 9 H); IR ($CHCl_3$) ν_{max}: 2145 cm^{-1}; MS (*m/z*): 338 (3), 337 (9), 336 (41), 335 (62), 334 (100), 322 (8), 321 (36), 320 (52), 319 (96), 237 (5), 152 (26), 115 (6), 73 (18%).

5-Ethyl-2-[(5-ethyl-2-thienyl)-ethynyl]-thiophene 11

^{1}H NMR ($CDCl_3$) δ: 7.07 (d, 1 H, J = 3.6 Hz), 6.65 (dt, 1 H, J_1 = 3.6 Hz, J_2 = 1.1 Hz), 2.82 (q, 2 H, J = 7 Hz), 1.31 (t, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ: 150.56, 132.52, 124.12, 120.87, 86.36, 23.85, 16.02; IR ($CHCl_3$) ν_{max}: 2145 cm^{-1}; MS (*m/z*): 248 (6), 247 (12), 246 (69), 233 (10), 232 (16), 231 (100), 229 (4), 217 (4), 216 (25), 171 (6), 145 (3), 123 (4), 115 (5), 109 (4), 108 (21%).

Biphenylacetylene 13

^{1}H NMR ($CDCl_3$) δ: 7.6 (m, 2 H), 7.4 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ: 133.11, 132.23, 129.05, 128.96, 128.85, 123.90, 89.96; IR ($CHCl_3$) ν_{max}: 2140 cm^{-1}; MS (*m/z*): 179 (15), 178 (100), 177 (10), 176 (19), 152 (9), 151 (7), 150 (5), 126 (4), 89 (8), 88 (4), 76 (10%).

Trimethylsilyl-(*o*-tolyl)acetylene 15

^{1}H NMR ($CDCl_3$) δ: 7.43 (m, 1 H), 7.19 (m, 3 H), 2.45 (s, 3 H), 0.27 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ: 141.14, 132.64, 129.87, 128.99, 125.95, 104.56, 98.58, 20.85, 0.25; IR ($CHCl_3$) ν_{max}: 2190 cm^{-1}; MS (*m/z*): 188 (41), 175 (7), 174 (27), 173 (100), 145 (26), 143 (15), 131 (6), 128 (6), 117 (6), 115 (8), 105 (6), 86 (12%).

Bi-(*o*-tolyl)acetylene 16

^{1}H NMR ($CDCl_3$) δ: 7.60 (m, 1 H), 7.29 (m, 3 H), 2.61 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ: 140.56, 132.52, 130.10, 128.83, 126.22, 123.95, 92.87, 21.25; IR ($CHCl_3$) ν_{max}: 2140 cm^{-1}; MS (*m/z*): 207 (16), 206 (100), 205 (80), 204 (20), 203 (20), 202 (20), 191 (29), 190 (17), 189 (21), 179 (7), 178 (17), 165 (14), 152 (5), 128 (6), 115 (6), 101 (12), 91 (12), 89 (13), 76 (5%).

5-[(2-Thienyl)ethynyl]thiophene-2-carbaldehyde 3

Compound 7 (1 g) was added to a mixture of DMF (424 mg) and $POCl_3$ (890 mg). The mixture was stirred at 60°C for 0.5 h. After cooling, an aqueous solution of AcONa was added and the mixture was extracted with Et_2O. The neutral extracts were dried (Na_2SO_4). Removal of the solvent gave a crude product that was chromatographed on SiO_2. Elution with $CHCl_3$/*n*-hexane 4:1 gave pure 3 (450 mg, 50%). ^{1}H NMR ($CDCl_3$) δ: 9.83 (s, 1 H), 7.66 (d, 1 H, J = 5 Hz), 7.38 (m, 2 H), 7.29 (d, 1 H, J = 5 Hz), 7.03 (dd, 1 H, J = [illegible] Hz); IR ($CHCl_3$) ν_{max}: 2720, 2200, 1670 cm^{-1}; MS (*m/z*): 220 (10), 219 (18), 218 (100), 217 (56), 190 (6), 189 (10), 145 (27), 95 (7), 87 (5%).

Desilylation of 5-trimethylsilyl-2-[(5-trimethylsilyl-2-thienyl)ethynyl)]-thiophene 9

Compound 9 (0.56 g, 1.66 mmoles) was added to a solution of 1 M KOH

(2.4 ml) in MeOH (3 ml) at 0°C. Acetonitrile wad added and the mixture was heated at 50°C. At the end of the reaction (tlc) the mixture was extracted with *n*-pentane. The neutral organic extracts were dried (Na_2SO_4). Removal of the solvent yielded pure 7. For spectra see above.

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