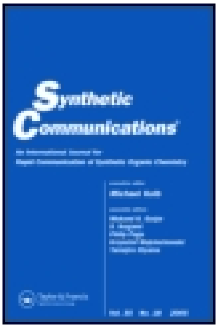

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A Synthetic Equivalent of 3,5-Dimethoxyphenyl Lithium. A Facile Route to 5-Substituted Resorcinols

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A SYNTHETIC EQUIVALENT OF 3,5-DIMETHOXYPHENYL LITHIUM. A FACILE ROUTE TO 5-SUBSTITUTED RESORCINOLS

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Summary: Butyl lithium metallates 1,3-dimethoxy-4,6-dichlorobenzene selectively at C-5. The resulting anion reacts effectively with electrophiles.

Hypericin is a naturally occurring octacyclic quinone which exhibits potent in vitro inhibitory activity against the human immunodeficiency virus (HIV) and other enveloped viruses such as the equine infectious anemia virus and the cytomegalovirus.[1] It has a mechanism of action different from antiviral agents presently used for the treatment of AIDS. Hypericin's antiviral activity is light dependent and it appears to affect the assembly of the virions.[2]

In the course of our evaluation of the effect of changes in structure on the biological activity of hypericin derivatives, we needed a readily available precursor to the 1,3-dihydroxyphenyl subunits contained in hypericin. A direct solution for the introduction of this

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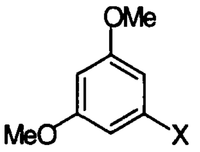
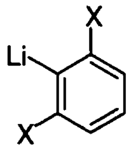
unit would be the organolithium reagent **1** or the Grignard reagent **2**. These reagents could be derived from the corresponding halide **3** . The bromide has been prepared in 20% yield[3] from 3,5-dimethoxyphenol and in 48% yield[4] from 3,5-dimethoxyaniline. Surprisingly, only the Grignard reagent **3** has been reported.[5] Recently, the triflate of 3,5-dimethoxyphenol has been employed in palladium-mediated substitution chemistry.[6] Direct metallation of 1,3-dimethoxybenzene affords only metallation at C-2.[7] Interestingly, 1,3-dichlorobenzene can also be metallated at C-2 and limited studies have shown that the anion reacts with electrophiles at -78 °C.[8]

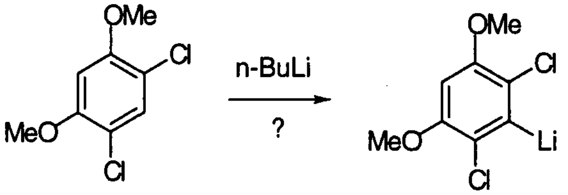


1: X = Li
2: X = MgX
3: X = Br, Cl



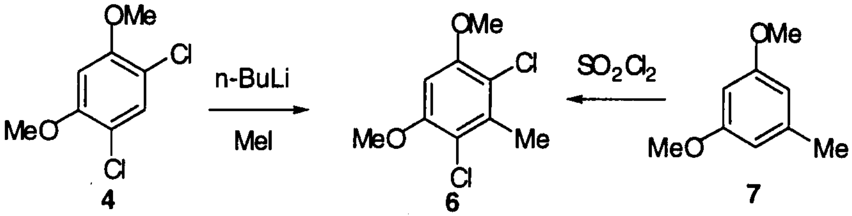
X = OMe, Cl

The selective metallations of 1,3-dimethoxybenzene and 1,3-dichlorobenzene led to the question of whether compound **4**, which contains both units, would yield anion **5**. Anion **5** represents a synthetic equivalent of **1**, provided that the chlorine atoms could be removed later under mild conditions.

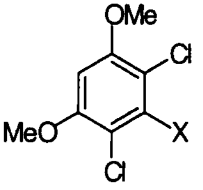


4 **5**

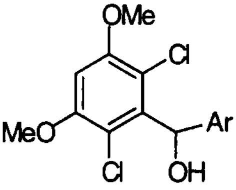
Compound **4** was prepared in 94% yield from 1,3-dimethoxybenzene by treatment with two equivalents of sulfuryl chloride in methylene chloride at 0 °C.[9] Metallation with n-butyl lithium (THF, -78 °C, 6 hr) and reaction at -78 °C with methyl iodide afforded an adduct which was identical to the product formed by treatment of **7** with sulfuryl chloride.



With the regiochemistry of metallation determined, anion **5** was next treated with a series of electrophiles. The reaction of anion **5** with ethyl formate and chlorotrimethylsilane produced **8** and **9** in yieds of 96% and 100%, respectively. The reaction of **5** with ethylene oxide afforded **10** in 95% yield. Interestingly, the reaction of **5** with aziridines failed. The reaction of **5** with benzaldehyde and **8** produced alcohols **11** and **12** in 89% and 90% yields, respectively.

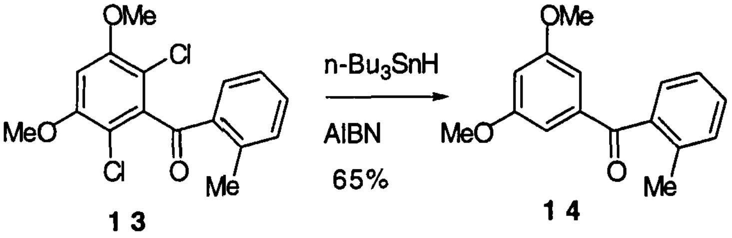


8: X=CHO
9: $X=SiMe_3$
1 0: $X=CH_2CH_2OH$



1 1: Ar=Ph
1 2: Ar=2,6-diCl-3,5-diOMeC_6H

Dechlorination could be efficiently achieved using tributyltin hydride and AIBN. An example is the dechlorination of **13** to produce **14**[10] in 65% yield.



13 **14**

The selective metallation of **4** followed by reaction with electrophiles and dechlorination constitutes a flexible way to synthesize 5-substituted resorcinols. Compound **14** will be employed in a synthesis of hypericin analogs.

EXPERIMENTAL

1,5-Dichloro-2,4-dimethoxybenzene (4):

Five grams of 1,3-dimethoxybenzene (0.036 mol) was dissolved in 50 mL of freshly distilled methylene chloride. The solution was then cooled to 0°C and SO_2Cl_2 (9.8g, 0.072 mol) was added to the reaction flask via a dropping funnel. The reaction mixture was then stirred for another 8 h, allowing the temperature to rise to rt. The solvent was removed in vacuo after the reaction was complete, affording 7.04 g of **4** as white crystals. (m.p. 119°C, 94% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.53 (s, 1H), 3.91 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 130.5, 114.0, 97.7, 56.5. IR (cm^{-1}): 3016, 2968, 2938, 2846, 1595, 1498, 1376, 1299, 1240, 1200, 1031. Anal. Calcd for $C_8H_8O_2Cl_2$: C, 46.41; H, 3.89. Found: C, 46.55; H, 3.82. HRMS (El) calcd for $C_8H_8O_2Cl_2$ (M^+) 205.9901, found (M^+) 205.9901.

General experimental procedures for the reaction between 4 and electrophiles.

To **4** (0.5 g, 2.415 mmol) dissolved in 20 mL of freshly distilled THF and cooled to -78°C under Ar was added 1.2 equivalents (2.90 mmol) of butyl lithium (1.22 mL of 2.38 M n-BuLi solution in hexanes) via a syringe dropwise. The mixture was then stirred for another 6 h at –78° C. The electrophile was added in one portion at –78°C. The reaction mixture was then allowed to warm to rt. Saturated NH_4Cl solution was added to quench the reaction. The mixture was then extracted with ether (3x30mL). The combined organic solution was washed with water and brine solution and dried over $MgSO_4$. Solvent was then removed in vacuo and the product was purified as described below for the individual compounds.

2,6-Dichloro-3,5-dimethoxytoluene (6):

Compound **6** was prepared from the reaction between **5** and methyl iodide (5 equiv.). After the usual work-up, **6** was obtained as a white crystal (m.p. 135°C, 100% yield). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.45 (s, 1 H), 3.91 (s, 6H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ:154.1, 136.1, 115.2, 95.1, 56.4, 17.9. IR (ν, cm^{-1}): 3009, 2968, 1578, 1460, 1341, 1212, 1083. MS: m/e 220 (M^+, 100), 177 (72), 142 127 (13), 111 (15), 77 (19), 41 (24). Anal. Calcd for $C_9H_{10}O_2Cl_2$: C, 48.90; H, 4.56. Found: C, 48.86; H, 4.43.

2,6-Dichloro-3,5-dimethoxybenzaldehyde (8):

Compound **8** was prepared from the reaction between **5** and ethyl formate (1 equiv.). Yellow solid was obtained with a yield of 96%. (m.p. 169-170°C). ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.45 (s, 1H), 6.71 (s, 1H), 3.96 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 189.8, 154.6, 132.3, 116.0, 100.4, 56.8. IR (v, cm^{-1}): 3014, 1707, 1577, 1434, 1330, 1214. Anal. Calcd for $C_9H_8O_3Cl_2$: C, 45.99; H, 3.40. Found: C, 46.98 H, 3.64. HRMS (EI) calcd for $C_9H_8O_3Cl_2$ (M$^+$) 233.9850, found (M$^+$) 233.9852.

1-Trimethylsilyl-2,6-dichloro-3,5-dimethoxybenzene (9):

Compound **9** was prepared from the reaction between **5** and TMSCl (2 equivs.) Silane **9** was obtained as a bright yellow crystal (m.p. 78°C, 99% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.58 (s, 1H), 3.90 (s, 6H), 0.51 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 154.2, 139.3, 120.4, 98.6, 56.6, 3.3. IR (v, cm^{-1}): 3012, 1573, 1464, 1393, 1288, 1206, 1045. MS m/e: 278 (M$^+$, 57), 263 (100), 248 (48), 233 (40), 213 (22) 197 (18), 175 (18), 135 (25), 115 (20), 93 (57), 77 (30), 65 (30), 44 (43). Anal. Calcd for $C_{11}H_{16}SiO_2Cl_2$: C, 47.31; H, 5.78. Found: C, 47.54; H, 5.67.

2-(2,6-Dichloro-3,5-dimethoxyphenyl) ethanol (10):

Compound **10** was prepared from the reaction between **5** and ethylene oxide. After the anion was formed, ethylene oxide gas was introduced to the reaction flask via a cooled syringe for 20 min. The reaction mixture was allowed to warm to rt followed by the usual work-up procedure. Crude product was then purified by flash chromatography on silica gel by using hexane/ethyl acetate (7:1) as the eluent. Pure **10** was obtained as a white crystal (m.p. 102°C, 95% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1 H), 3.91 (s, 6H), 3.83-3.89 (q, 2H), 3.28-3.32 (t, 2H), 1.47 (t, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 136.6, 115.3, 95.8, 61.0, 56.5, 34.9. IR (v, cm^{-1}): 3620, 3012, 1578, 1453, 1433, 1341, 1213,1081. Anal. Calcd for $C_{10}H_{12}O_3CI_2$: C, 47.83; H, 4.82. Found: C, 47.80; H, 4.67. HRMS (El) calcd for $C_{10}H_{12}O_3CI_2$ (M^+) 250.0163, found (M^+) 250.0162.

2,6-Dichloro-3,5-dimethoxyphenyl) phenyl carbinol (11):

Compound **11** was prepared from the reaction between **5** and benzaldehyde (1.2 equiv.) and was purified by flash chromatography on silica gel using hexane/ethyl acetate (15:1) as the eluent. Pure compound **11** was obtained as a yellow liquid (89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.31 (m, 5H), 6.68-6.72 (d, 1H), 6.57 (s, 1H), 3.94 (s, 6H), 3.62-3.66 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 141.5, 139.3, 128.2, 127.1, 125.3, 114.7, 96.7, 72.8, 56.5. IR (cm^{-1}): 3568, 3014, 2968, 1581, 1455, 1432, 1330, 1208. MS: m/e 312 (M^+, 100), 295, 276, 259, 240, 162, 139, 105, 79, 51.

Di-(2,6-dichloro-3,5-dimethoxyphenyl) carbinol (12):

Compound **12** was prepared from the reaction between **5** and **8** (1.2 equiv.). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent. Alcohol **12** was obtained as white crystals. (m.p. 243°C, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87-6.91 (d, 1 H), 6.54 (s, 2H), 3.90 (s, 12H, 3.79-3.83 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 137.8, 116.0, 96.3, 74.8, 56.6. IR (v, cm^{-1}): 3014, 1577, 1427, 1327, 1210. MS: m/e 442 (M^+, 57), 425 (18), 407 (83), 390

(32), 370 (100), 339 (15). Anal. Calcd for $C_{17}H_{16}O_5Cl_4$: C, 46.18; H, 3.65. Found: C, 46.38; H, 3.54.

3,5-Dimethoxy-2'-methylbenzophenone (14):

Compound **13** was prepared from PCC oxidation of product from reaction between **5** and 2-methylbenzaldehyde. Pure **13** was obtained as a white solid (m.p. 178°C) after purification by flash chromatography on silica gel using hexane/ethyl acetate (9:1) as the eluent (85% overall yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.14-7.46 (m, 4H), 6.59 (s, 1 H), 3.93 (s, 6H), 2.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 154.9, 141.4, 140.2, 134.3, 133.1 ,132.5, 132.4, 126.0, 111.2, 97.5, 56.6, 22.1. HRMS (EI) calcd for $C_{16}H_{14}O_3Cl_2$ (M^+) 324.0320, found (M^+) 324.0322.

To 0.1g of **13** dissolved in 20 mL of freshly distilled benzene and heated to boiling was added 0.409 g of n-Bu_3SnH and 0.210 g of AIBN together in 5 mL benzene. Solution of AIBN/n-Bu_3SnH 0.5 mL was added to boiling benzene in the reaction flask every 30 min. The reaction mixture was then boiled for another 8 hours after the addition was complete. After the reaction mixture was cooled, benzene was removed by vacuo and **14** was purified by flash chromatography on silica gel (hexane : ethyl acetate = 20:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.11-7.53 (m, 6H), 6.61 (d, J = 1.8 Hz, 1H), 3.94 (s, 6H), 2.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 147.6, 141.3, 137.8, 135.8 132.5, 129.9, 125.6, 121.3, 110.9, 94.7, 57.1, 25.0. HRMS (EI) calcd for $C_{16}H_{16}O_3$ (M^+) 256.1099, found (M^+) 256.1098.

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