Synthesis, Stability, and Reactions of 2,6-Dichlorophenyllithium

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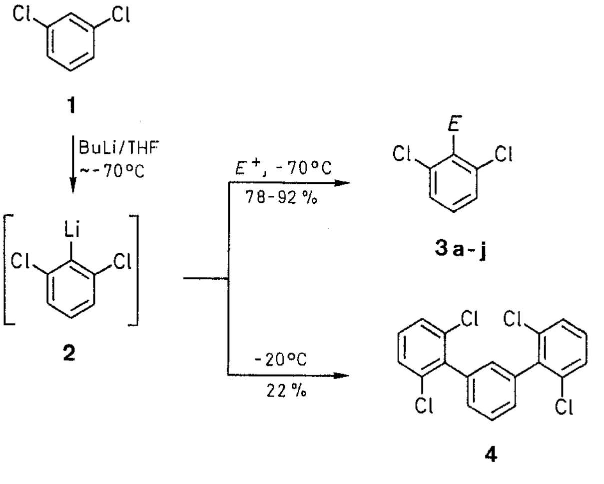
A convenient, general, and regioselective synthesis of 2,6-dichloroaromatic compounds from *m*-dichlorobenzene is described. The stability of 2,6-dichlorophenyllithium is examined.

An array of physiologically active compounds containing the 2,6-dichlorophenyl substitution pattern have been reported. These substances have displayed activity as herbicides,[1] antibacterials,[2] and anti-hypertensives.[3] Although the preparation of 2,6-difluorophenyllithium and its conversion to 2,6-difluoroaromatic compounds is well documented,[4] a similar detailed study on 2,6-dichlorophenyllithium has not been published. Herein we report a practical, high yielding, and regioselectice procedure for the preparation of 2,6-dichlorophenyllithium and its conversion to 2,6-dichloroaromatic compounds via the direct metalation of *m*-dichlorobenzene with *n*-butyllithium.

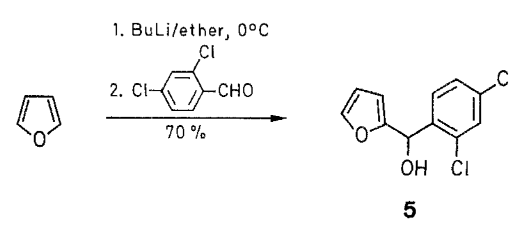
Treatment of *m*-dichlorobenzene (**1**) in tetrahydrofuran at − 50 to − 70 °C with one equivalent of *n*-butyllithium in hexane afforded 2,6-dichlorophenyllithium (**2**) as a finely dispersed white solid, which on reaction with an appropriate electrophile gave the 2,6-dichloro substituted benzenes **3** in good yield (see Scheme **A** and Table). The identity of each product **3a–j** was determined by elemental analysis, spectroscopic data (^{1}H-NMR, MS), or comparison with an authentic sample.



Scheme A

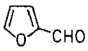
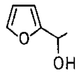
Of major concern using this procedure was the stability of **2** because of its potential as a precursor to a polychlorinated biphenyl or terphenyl. Based on the reaction yields and physical characteristics, **2** appeared to be quite stable between − 50 to − 70 °C. However, upon slow warming of a reaction mixture of **2** in THF, darkening began at − 45 °C and at − 20 °C a highly exothermic reaction occurred affording a black sludge. Chromatographic work-up of this mixture gave one major organic product in 22 % yield, which was characterized as the terphenyl **4** based on microanalysis and spectral data. Product **4** probably arises by consecutive loss of lithium chloride and trapping of the intermediate aryne by **2**. The presence of **4** as an impurity in the products **3a–j** was then examined. As a model case, the furyl alcohol **3a** was prepared at − 50 °C and at − 70 °C and carefully analyzed (HPLC and GC) for the presence of **4**. The product formed at − 70 °C showed no trace of **4** but **3a** generated at − 50 °C contained a new impurity (0.1 area %) with the same retention time as **4**. Thus, to avoid the formation of **4** one should carry out these reactions at − 70 °C or less.

Another area of concern in the metalation of **1** was the regioselectivity since exchange could also potentially occur at



Scheme B

Table. 2,6-Dichloro Substituted Derivatives **3a–j** Prepared

Electrophile	*E* in **3**	Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	MS[e] m/z (M^+)
		**3a**	90[f]	oil	$C_{11}H_8Cl_2O_2$ (243.1)	3.47 (d, 1H, OH, J = 10); 6.18 (d, 1H, 3-H_{furyl}, J = 3); 6.38 (dd, 1H, 4-H_{furyl}, J = 3,2); 6.58 (d, 1H, CH, J = 10); 7.22 (m, 2H_{arom}); 7.37 (m, 2H_{arom})	242/244
PhCOPh	$Ph_2C(OH)$	**3b**	85[g]	114–116	$C_{19}H_{14}Cl_2O$ (329.2)	4.82 (s, 1H, OH); 7.30 (m, 13H_{arom})	328/330
PhCHO	PhCH(OH)	**3c**	92[f]	oil	$C_{13}H_{10}Cl_2O$ (253.1)	3.41 (d, 1H, OH, J = 11); 6.64 (d, 1H, CH, J = 11); 7.28 (m, 8H_{arom})	252/254
$ClCO_2Et$	CO_2Et	**3d**	82[f]	oil	$C_9H_8Cl_2O_2$ (219.1)	1.43 (t, 3H, CH_3, J = 6); 4.47 (q, 2H, CH_2, J = 6); 7.30 (m, 3H_{arom})	218/220
Me_2NCHO	CHO	**3e**	84[f]	68–70	$C_7H_4Cl_2O$ (175.0)	7.41 (s, 3H_{arom}); 10.55 (s, 1H, CHO)	174/176 173/175 (100%)
S/$PhCH_2Br$	SCH_2Ph	**3f**	80[h]	oil	$C_{13}H_{10}Cl_2S$ (269.2)	4.10 (s, 2H, CH_2); 7.14 (t, 1H, 4-H_{arom}, J = 7); 7.20 (s, 5H, C_6H_5); 7.35 (d, 2H, 3,5-H_{arom}, J = 7)	268/270
$ClSiMe_3$	$SiMe_3$	**3g**	90[f]	oil	$C_9H_{12}Cl_2Si$ (219.2)	0.44 (s, 9H, CH_3); 7.08 (m, 1H, 4-H_{arom}); 7.16 (m, 2H, 3,5-H_{arom})	218/220 203/205 (100%)
CH_3I	CH_3	**3h**	85[h]	oil	$C_7H_6Cl_2$ (161.0)	2.48 (s, 3H, CH_3); 7.05 (t, 1H, 4-H_{arom}, J = 7); 7.28 (d, 2H, 3,5-H_{arom}, J = 7)	160/162
$(CO_2Et)_2$	$COCO_2Et$	**3i**	78[f]	oil	$C_{10}H_8Cl_2O_3$ (247.1)	1.39 (t, 3H, CH_3, J = 6); 4.41 (q, 2H, CH_2, J = 6); 7.36 (s, 3H_{arom})	246/248 173/175 (100%)
PhCN	PhC=NH	**3j**	90[i]	62–64	$C_{13}H_9Cl_2N$ (250.1)	7.28 (m, 1H_{arom}); 7.41 (m, 5H, C_6H_5); 7.74 (br d, 2H_{arom}, J = 6); 9.72, 10.87 (br s, 1H, NH, *syn*/*anti*, 1/5)	249/251

[a] Yields refer to chromatographed or crystallized product.
[b] Melting points were determined on a Thomas-Hoover apparatus and are uncorrected.
[c] Satisfactory microanalyses obtained: C, H ±0.40.
[d] The ^{1}H-NMR spectra were recorded on a General Electric QE-300 spectrometer.
[e] The mass spectra were taken on a Model 21-110 Consolidated Electrodyne Corp. spectrometer.
[f] Purified by flash chromatography on silica gel (solvent): **3a** (toluene/EtOAc, 98 : 2), **3c** (toluene/EtOAc, 3 : 1), **3d** and **3i** (toluene/EtOAc, 1 : 1), **3e** and **3g** (toluene).
[g] Compound **3b** was crystallized from hexane/toluene (95 : 5).
[h] Purified by distillation: **3f**, bp 185–187 °C/2 mbar; **3h**, bp 51–52 °C/2 mbar.
[i] Compound **3j** was slurried in hexane, filtered, and dried.

position 4 or 6. An authentic sample of the regioisomer of **3a**, 1-(2,4-dichlorophenyl)-1-(2-furyl)methanol (**5**) was prepared by condensation of 2-furyllithium with 2,4-dichlorobenzaldehyde (Scheme **B**). HPLC examination of **3a** formed at either − 50 °C or − 70 °C displayed no trace of **5**. Thus, the metalation appears to occur selectively at position 2.

In conclusion, the procedure described here is a general, high yielding, and regioselective method for the synthesis of 2,6-dichloroaromatic compounds.

2,6-Dichlorophenyl Derivatives 3a–j; General Procedure:

To a solution of **1** (4.41 g, 30 mmol) in dry THF (75 mL) at − 70 °C in a 250 mL flask equipped with a thermometer, paddle stirrer is added a 1.6 M hexane solution of BuLi (19 mL, 30 mmol) over 1 h under N_2, while keeping the temperature between − 65 to − 70 °C. The slurry is stirred for 45 min, then a solution of the electrophile (30 mmol, see Table) in THF (25 mL) is added dropwise over 1 h at − 65 to − 70 °C. The resulting mixture is stirred for 45 min at − 70 °C, the cooling bath is removed, and the temperature is allowed to rise to − 20 °C. A solution of NH_4Cl (4 g) in water (75 mL) is then added over 5 min followed by EtOAc (75 mL) and brine (30 mL). The mixture is transferred to a separatory funnel, the organic phase is separated, washed with water (2 × 50 mL), dried ($MgSO_4$), filtered, evaporated to dryness, and the residue is purified by either flash chromatography or recrystallized (see Table).

1,3-Bis(2,6-dichlorophenyl)benzene (4):

A slurry of **2** (25 mmol) is prepared as described in the general procedure for the preparation of **3a–j**. Instead of adding an electrophile, the slurry is allowed to warm slowly from − 70 to − 20 °C. At − 45 °C, the mixture darkens slightly, at − 25 °C it becomes black, and at − 20 °C an exothermic reaction ensues increasing the temperature to + 5 °C within seconds. The resulting black sludge is diluted with a solution of NH_4Cl (2 g) in water (50 mL) followed by ether (25 mL). The organic phase is separated, washed with water (25 mL), dried ($MgSO_4$), filtered, and evaporated affording a black oil. TLC on silica gel (hexane) shows one main spot (UV visualization) with $R_f = 0.5$ in addition to a large amount of material remaining at the origin. Flash chromatography on silica gel (hexane as eluent) gives after evaporation of the solvent, a white crystalline solid; yield: 670 mg (22%); mp 128–129 °C.

$C_{18}H_{10}Cl_4$	calc.	C 58.74	H 2.74
(368.1)	found	58.58	2.94

MS: m/z (%) = 368 (M^+, 100, four chlorine atom isotope cluster); 296 (29, two chlorine atom isotope cluster).

IR ($CHCl_3$): ν = 3011, 1590, 1579, 1455, 1251, 1220, 1151, 1107, 1089, 1028 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 203 (4.79).

^1H-NMR ($CDCl_3$/TMS): δ = 7.56 (t, 1 H, 4-H_{arom}, J = 7.8 Hz); 7.40 (d, 4 H, 3′,3′,5′,5′-H_{arom}, J = 7.8 Hz); 7.32 (dd, 2 H, 3,5-H_{arom}, J = 1.8, 7.8 Hz); 7.22 (m, 3 H, 4′,4′,1-H_{arom}).

1-(2,4-Dichlorophenyl)-1-(2-furyl) methanol (5):

A solution of furan (1.82 mL, 25 mmol) in ether (100 mL) under N_2 is stirred at 0 °C and a 1.65 M hexane solution of BuLi (15.15 mL, 25 mmol) is added dropwise over 20 min. The mixture is stirred for 2 h, and a solution of 2,4-dichlorobenzaldehyde (4.37 g, 25 mmol) in ether (20 mL) is added dropwise. The mixture is allowed to come to room temperature and a 5 % aq. solution of NH_4Cl (70 mL) is added, and the phases are separated. The ether layer is washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated affording 5.2 g of a pale yellow oil. The crude product is chromatographed on silica gel (1 : 1 toluene/EtOAc as eluent) giving 4.25 g (70 %) of pure **5** as an oil; yield: 4.25 g (70 %).

$C_{11}H_8Cl_2O_2$	calc.	C 54.35	H 3.32	Cl 29.17
(242.1)	found	54.38	3.22	28.93

MS: m/z (%) = 242 (M^+, 100); 244 (33).

IR ($CHCl_3$): ν = 3603, 1591, 1564, 1472, 1382, 1011 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 294 (1.91), 280 (2.58), 272 (2.65), 263 (2.59).

^1H-NMR ($CDCl_3$/TMS): δ = 3.00 (br s, 1 H, OH); 6.05 (d, 1 H, 3-H_{furyl}, J = 6.0 Hz); 6.12 (s, 1 H, CH); 6.30 (dd, 1 H, 4-H_{furyl}, J = 2.3, 4.6 Hz); 7.30 (dd, 1 H, 5-H_{arom}, J = 2.2, 8.0 Hz); 7.36 (d, 1 H, 3-H_{arom}, J = 2.2 Hz); 7.38 (d, 1 H, 5-H_{furyl}, J = 2.2 Hz); 7.6 (d, 1 H, 6-H_{arom}, J = 8.0 Hz). (The chemical shift assignments of 5-H_{furyl} and 3-H_{arom} were determined by a decoupling experiment).

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