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A new efficient synthesis of *ortho*-cyanoarenes via directed lithiation followed by electrophilic cyanation

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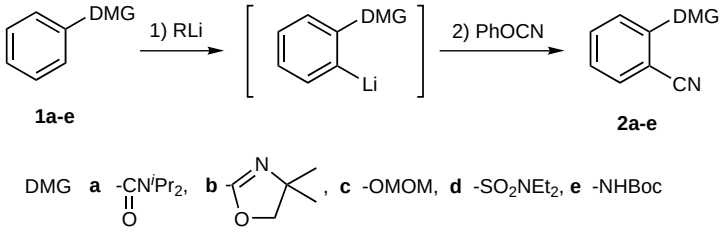
Abstract—A one-pot procedure for the conversion of mono-substituted arenes into the *ortho*-cyano derivatives was accomplished through directed lithiation followed by electrophilic cyanation with phenyl cyanate.

The introduction of a cyano group to arenes is occasionally achieved by using CCl_3CN, BrCN or Hg(ONC).[1] For example, secondary aromatic amines as well as phenols were cyanated in the *ortho* position on treatment with BCl_3 followed by CCl_3CN.[2] We now wish to report a more efficient synthesis of *ortho*-cyanobenzenes via directed lithiation and succeeding electrophilic cyanation (Scheme 1).

The cyanation through carbon–carbon bond formation is usually effected by the nucleophilic attack of a cyanide ion (CN^-) at an electrophilic carbon, while several reagents conduct like cyano cation (CN^+) equivalents on treatment with a carbanion. These include $(CN)_2$,[3] ClCN,[4] tosyl cyanide,[5] phenyl cyanate,[6] 2-chlorobenzyl thiocyanate,[7] pentachlorobenzonitrile,[8] 1-cyanobenzotriazole[9,10] and 1-cyanoimidazole.[11] In terms of safety and accessibility of reagent, the utilization of phenyl cyanate (PhOCN) which is easily prepared from phenol and BrCN[6,12] was focused in the current study. As a matter of practical convenience, this liquid reagent can be directly added via a syringe without dissolution in any solvent to the solution of lithio compound.

N,*N*-Diisopropylbenzamide (**1a**) was lithiated with *t*-BuLi in THF below −70°C for 1 h,[13] and the resulting 2-lithobenzamide was immediately treated with PhOCN at this temperature. The mixture was stirred for 30 min and allowed to warm to 0°C during 2 h. After hydrolysis, extraction with dichloromethane and further workup, the crude product was purified by silica gel chromatography and subsequent Kugelrohr distillation to give 2-cyanobenzamide **2a** in 98% yield[14] (entry 1 in Table 1). The use of 4-nitrophenyl cyanate[15] and 1-cyanoimidazole[11] instead of PhOCN under comparable conditions also afforded the cyanobenzamide **2a** although in low yields such as 23 and 52%, respectively. The other benzenes bearing a directed metalation group (DMG) were similarly subjected to the lithiation/cyanation (entries 2–5), in which each lithiation was performed according to the procedure in literature[13,16,17] including the metalation of **1a**.



Scheme 1.

Keywords: directed lithiation; electrophilic cyanation; phenyl cyanate; nitriles.

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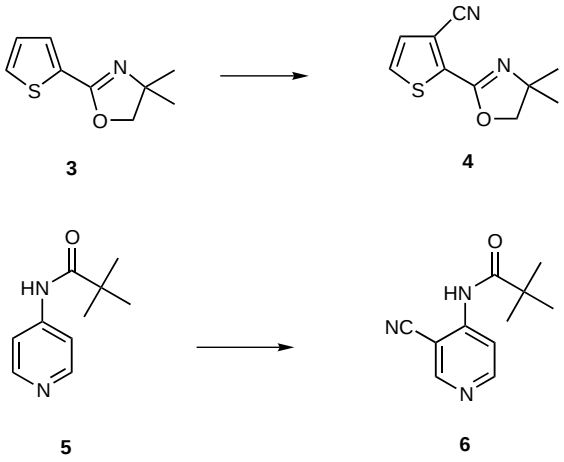
Table 1. Synthesis of *ortho*-cyanoarenes

Entry	Substrate	Lithiation conditions[a]	Product	Yield (%)[b]
1	**1a**	^{t}BuLi, THF (10 mL), ≤ -70°C, 1 h	**2a**	98
2	**1b**	^{t}BuLi, ether (3 mL), ≤ -70°C, 1 h	**2b**	73
3	**1c**	^{t}BuLi, ether (3 mL), 0°C, 1 h	**2c**	78
4	**1d**	^{n}BuLi, THF (2 mL), 0°C, 0.5 h	**2d**	64
5	**1e**	^{t}BuLi,[c] ether (3 mL), -10°C, 3 h	**2e**	68
6	**3**	^{n}BuLi, ether (10 mL), ≤ -70°C, 0.25 h and then 0°C, 0.5 h	**4**	85
7	**5**	^{n}BuLi,[c] THF (3 mL), 0°C, 3 h	**6**	47

[a] Lithiation was performed by treatment of the substrate (1.0 mmol) in THF or ether, which are shown together with the requisite volume, with commercial BuLi solution (1.1 mmol unless otherwise noted).
[b] Isolated yields of pure material after silica gel chromatography.
[c] BuLi (2.1 mmol) used.



Scheme 2.

This cyanation method was successfully applied to heteroarenes (Scheme 2), i.e. 2-oxazolinylthiophene[18] (**3**) and *N*-pivaloyl 4-aminopyridine[19] (**5**) were converted into the corresponding *ortho*-cyano derivatives **4** and **6** (entries 6 and 7).

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14. Compound **2a** was obtained as colorless needles (hexane), mp 107–108°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (d, 6H, $J=6.2$ Hz), 3.59 (septet, 2H, $J=6.7$ Hz), 7.34 (ddd, 1H, $J=7.7$, 1.2, 0.6 Hz); 7.45 (td, 1H, $J=7.7$, 1.2 Hz), 7.62 (td, 1H, $J=7.7$, 1.3 Hz); 7.68 (ddd, 1H, $J=7.8$, 1.3, 0.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.3 (0.5C), 20.7 (0.5C), 46.3 (0.5C), 51.5 (0.5C), 109.2, 116.8 (C≡N), 125.8, 128.6, 132.9, 133.0, 142.6, 166.8; IR (KBr) ν_{max} 2226 cm^{-1} (C≡N); EI MS (m/z) 230 (M^+, 12%), 215 (14), 187 (46), 173 (37), 147 (7), 130 (100), 102 (57).
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