ORTHO-LITHIATION OF PHENOLS USING THE BIS(DIMETHYLAMINO)PHOSPHORYL GROUP AS A DIRECTING GROUP

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Aryl tetramethylphosphorodiamidates were effectively lithiated with *sec*-BuLi at -105°C to give *ortho*-lithiated species which provide *ortho*-substituted phosphates by treatment with a variety of electrophiles.

KEYWORDS lithiation; phenol; bis(dimethylamino)phosphoryl group; phosphate; aryl tetramethylphosphorodiamidate

Heteroatom-facilitated *ortho*-lithiation reaction is used increasingly in the regioselective construction of highly substituted aromatic compounds.¹⁾ After the discovery that anisole could be *ortho*-lithiated,²⁾ the directed lithiation of phenols using tetrahydropyran,^{1a,3)} methoxymethyl,^{1a,1d,4)} and carbamates⁵⁾ as masking and activating groups have been investigated. *ortho*-Lithiation of unmasked phenol has also been reported.^{3b,6)} Among these directors, the methoxymethyl and carbamate groups show effective lithiation abilities and have been applied to the synthesis of natural products.^{5b,7)} We report here on a new and powerful director, bis(dimethylamino)phosphoryl group, for phenols. Its potential as director was revealed by the intermolecular competition with other masked phenol metalation directors.

The *ortho*-lithiation of phenyl diethylphosphate (1) using LDA at -78°C has already been reported.⁸⁾ However, rapid $\text{O} \rightarrow \text{C}$ 1,3-diethylphosphoryl migration of the lithiated species (3) to give diethyl 2-hydroxyphenylphosphonate (5) prevented the introduction of electrophiles into this intermediate.⁸⁾ Since aryl phosphate derivatives are readily available⁸⁾ and phosphoryl groups are removable⁹⁾ under acidic

Table I. Synthesis of *ortho*-Substituted Phenyl Tetramethylphosphorodiamidates (7)

Run	Electrophile (E^+)	Product (7)	Yield (%)	mp (bp) $^{\circ}\text{C}$
E				
1	MeI	7a Me	87	(111/0.5)
2	Me_3SiCl	7b Me_3Si	79	64–65
3	$(\text{PhS})_2$	7c PhS	64	(160/0.6)
4	<i>p</i> -MeO-C ₆ H ₄ -CHO	7d <i>p</i> -MeO-C ₆ H ₄ -CH(OH)	67	114–116
5	PhCOPh	7e Ph-C(OH)-Ph	72	138–139
6	<i>p</i> -MeO-C ₆ H ₄ -COCl	7f <i>p</i> -MeO-C ₆ H ₄ -CO	94	oil

conditions to regenerate the parent phenols, we examined their potential for the *ortho*-lithiation reaction. First, we reexamined the lithiation of **1** at low temperatures (Chart 1). However, only a migration⁸⁾(**5**; 94% yield) was observed even upon treatment of **1** with *sec*-BuLi in THF at -105°C for 1 h followed by quenching with a saturated NH_4Cl solution at -105°C . The bis(dimethylamino)phosphoryl group as a director has recently been used for the lithiation of tetrahydroisoquinolines^{9a)} and furanols.^{9b)} Therefore, we examined the lithiation of aryl tetramethylphosphorodiamidates as follows. Phenyl tetramethylphosphorodiamidate (**2**) was lithiated by a 1.2 eq of LDA or *sec*-BuLi at -78°C for 1 h to give an analogous migration product (**6**) in 80% or 78% yield after standard workup. Although lithiated species (**4**), generated at -105°C , was quenched with an NH_4Cl solution at -78°C to give **6** in 42% yield, the starting material (**2**) was completely recovered if the quenching was carried out at -105°C . The above results suggest that the migration of the bis(dimethylamino)phosphoryl group in **4** is slower than that of the diethylphosphoryl group in **3** and that quenching at -105°C may be required for the introduction of electrophiles into the lithiated species **4** without migration. When **2** was lithiated by 1.2 eq of *sec*-BuLi at -105°C for 1 h followed by quenching with 1.5 eq of MeI at -105°C , the expected methylated compound (**7a**) was obtained in high yield (Table I; Run 1). Satisfactory yields were obtained using TMSCl (Run 2), aldehyde (Run 4), keton (Run 5), and acid chloride (Run 6) as electrophiles.

Regioselective methylation was achieved by the reaction of methoxy-substituted phenyl phosphorodiamidates (**8a-d**) with MeI under the lithiation conditions described above to give **10a-d** in high yields (Chart 2). The regiochemistry of **10a-d** were reliably determined by 400 MHz ^1H -NMR spectroscopy.¹⁰⁾ In the cases of *m*-methoxy-substituted phosphorodiamidates (**8b** and **8d**), exclusive methylation at the position between the phosphate and methoxy groups was effected, and no regioisomer was detected. In a similar manner, 1-naphthyl phosphorodiamidate (**9**) was methylated to give a 2-methylated compound (**11**).

Table II. Intermolecular Competitions of Lithiation

Run	Compound	Methylated product (yield, %)		Starting material (yield, %)	
1	8c + 12a	10c ; 76.9	13a ; 21.9	8c ; <1	12a ; 71.9
2	8c + 12b	10c ; 65.1	13b ; 33.9	8c ; 23.4	12b ; 61.0

Next, intermolecular competition¹¹⁾ between **8c** and other aromatic derivatives (**12a** and **b**) bearing well-directed metalation groups (DMG), were examined (Chart 3). The lithiated species, generated by the action of 1.0 eq of *sec*-BuLi at -105°C, were trapped by adding MeI. After chromatographic separation of the phosphate and other DMG derivatives, the methylation ratio was analyzed by GC. As can be seen from Table II (Runs 1 and 2), **8c** directs *ortho*-lithiation better than dose (methoxymethoxy)benzene (**12a**)^{1a,ld,4)} or phenyl *N,N*-diethylcarbamate (**12b**).⁵⁾

Removal of the bis(dimethylamino)phosphoryl group was easily achieved. For example, hydrolysis^{9b)} (HCOOH/reflux/1 h) of **7a** or **11** afforded *o*-cresol or 2-methyl-1-naphthol in quantitative or 87.6% yield. The behavior of tetramethylphosphorodiamidate as a latent directed metalation group^{11c)} was demonstrated by the reaction of **7e** with sodium in liquid ammonia¹²⁾ to give triphenylmethanol in 92% yield.

The above results indicate that the aryl tetramethylphosphorodiamidate is a powerful directed lithiation group which has the added advantages of being easily convertible into *ortho*-substituted phenols by hydrolysis and into substituted aromatics by reductive dehydroxylation. Application of the method to the synthesis of natural products is currently under investigation.

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