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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 carbamates[5)] 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 O→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 available[8)] and phosphoryl groups are removable[9)] under acidic

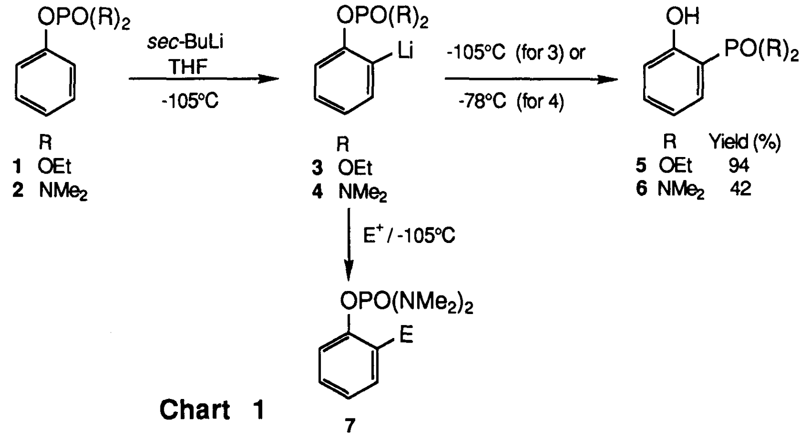
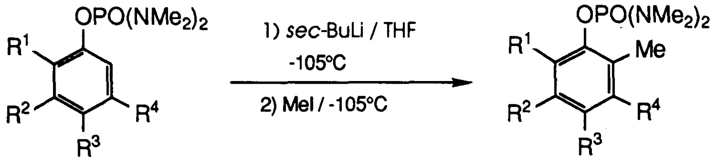


Chart 1

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

Run	Electrophile (E^+)	Product (**7**)	E	Yield (%)	mp (bp) °C
1	MeI	**7a**	Me	87	(111/0.5)
2	Me_3SiCl	**7b**	Me_3Si	79	64-65
3	$(PhS)_2$	**7c**	PhS	64	(160/0.6)
4	p-MeO-C_6H_4-CHO	**7d**	p-MeO-C_6H_4-CH(OH)	67	114-116
5	PhCOPh	**7e**	Ph-C(OH)-Ph	72	138-139
6	p-MeO-C_6H_4-COCl	**7f**	p-MeO-C_6H_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$_4$Cl solution at -105 °C. The bis(dimethylamino)phosphoryl group as a director has recently been used for the lithiation of tetrahydroisoquinolines9a) 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$_4$Cl 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.

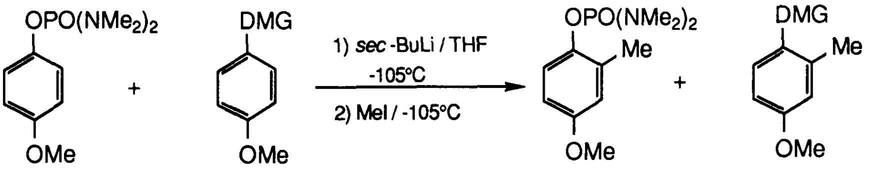


	R^1	R^2	R^3	R^4
8a	OMe	H	H	H
8b	H	H	H	OMe
8c	H	H	OMe	H
8d	H	OMe	H	OMe
9	-(CH=CH)$_2$-		H	H

Chart 2

	R^1	R^2	R^3	R^4	Yield (%)
10a	OMe	H	H	H	87
10b	H	H	H	OMe	75
10c	H	H	OMe	H	91
10d	H	OMe	H	OMe	93
11	-(CH=CH)$_2$-		H	H	87

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 ^{1}H-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**).



8c

DMG
12a OCH$_2$OMe
12b OCONEt$_2$

10c

DMG
13a OCH$_2$OMe
13b OCONEt$_2$

Chart 3

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,1d,4) or phenyl N,N-diethylcarbamate (**12b**).5)

Removal of the bis(dimethylamino)phosphoryl group was easily achieved. For example, hydrolysis9b) (HCOOH/reflux/1 h) of **7a** or **11** afforded o-cresol or 2-methyl-1-naphthol in quantivative or 87.6% yield. The behavior of tetramethylphosphorodiamidate as a latent directed metalation group11c) 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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