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LITHIATION OF <u>ORTHO</u>-TOLYL TETRAMETHYLPHOSPHORODIAMIDATES: A FACILE SYNTHESIS OF 2-ARYLBENZOFURANS INCLUDING NEOLIGNAN, CARINATIN

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ortho-Tolyl tetramethylphosphorodiamidates were lithiated with sec-BuLi at -105 °C to give corresponding benzylic lithio species which underwent reaction with electrophiles. When benzoates were used as electrophiles, deoxybenzoin derivatives were obtained. Acidic treatment of these products in refluxing formic acid gave 2-arylbenzofurans. The neolignan, carinatin, was successfully synthesized using this methodology.

KEYWORDS lithiation; ortho-cresol; bis(dimethylamino)phosphoryl group; phosphate; ortho-tolyl tetramethylphosphorodiamidate; 2-arylbenzofuran; neolignan; carinatin

In the context of masked phenol-directed metalation, lithiation of ortho-cresol derivatives (**1**-**3**)[1)] as shown in Chart 1 has been investigated. In general, these metalations are complicated by competing ring and ortho-methyl deprotonations. For example, lithiation (tert-BuLi, cyclohexane, reflux in 10 h) of 2-methylanisole (**1**) affords two compounds resulting from ring and benzylic metalations in 34% and 47% yields, respectively.[1b)] In the lithiation (tert-BuLi, hexane, 0 °C for 1 h) of 2-(methoxymethoxy)toluene (**2**), ring metalation was exclusively observed in high yield and there was no benzylic metalation.[1d)] Aromatic vs. ortho-methyl proton abstraction selectivity was also influenced by the metalation conditions such as the base (sec-BuLi/N,N,N',N'-tetramethylenediamine (TMEDA) or lithium diisopropylamide (LDA), -78 °C for 1 h) employed for the matalation of (2-methylphenyl)carbamate (**3**).[1e)] Previously, we reported[2)] that bis(dimethylamino)phosphoryl group [$-PO(NMe_2)_2$] is a powerful metalation director generating ortho-lithiated species of aryl tetramethylphosphorodiamidates [$ArO-PO(NMe_2)_2$] at -105 °C. We report here the directed lithiation of ortho-tolyl tetramethylphosphorodiamidates (**4**) and demonstrate its utility for the regioselective synthesis of 2-arylbenzofurans[3)] including a natural product, carinatin.[4)]

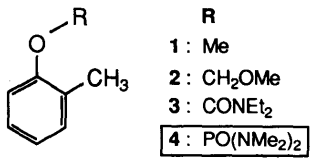


Chart 1

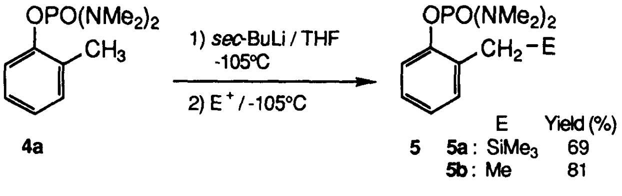


Chart 2

Lithiation of phosphate **4a** with 1.2 eq of sec-BuLi in THF at -105 °C for 1 h resulted in the formation of the corresponding benzylic anion, which upon treatment with electrophiles (Me_3SiCl and MeI) and quenching with sat. NH_4Cl at -90 °C gave **5a**, **b** in good yields (Chart 2). None of the isomers resulting from ring metalation of **4a** appeared.

A number of synthesis methods of 2-arylbenzofurans have been described.[3)] Among them,

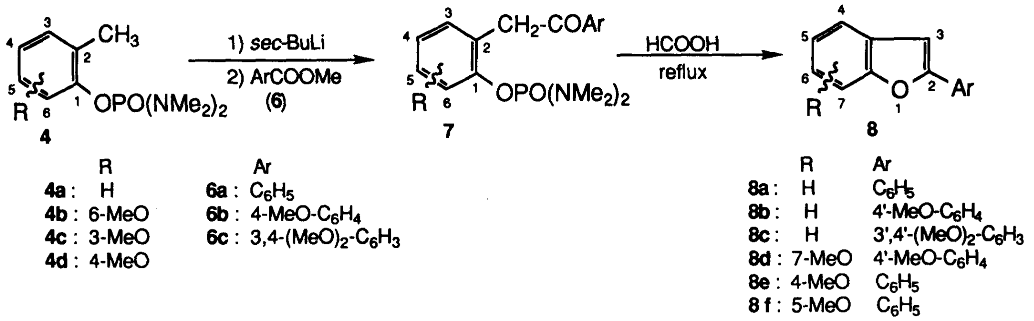


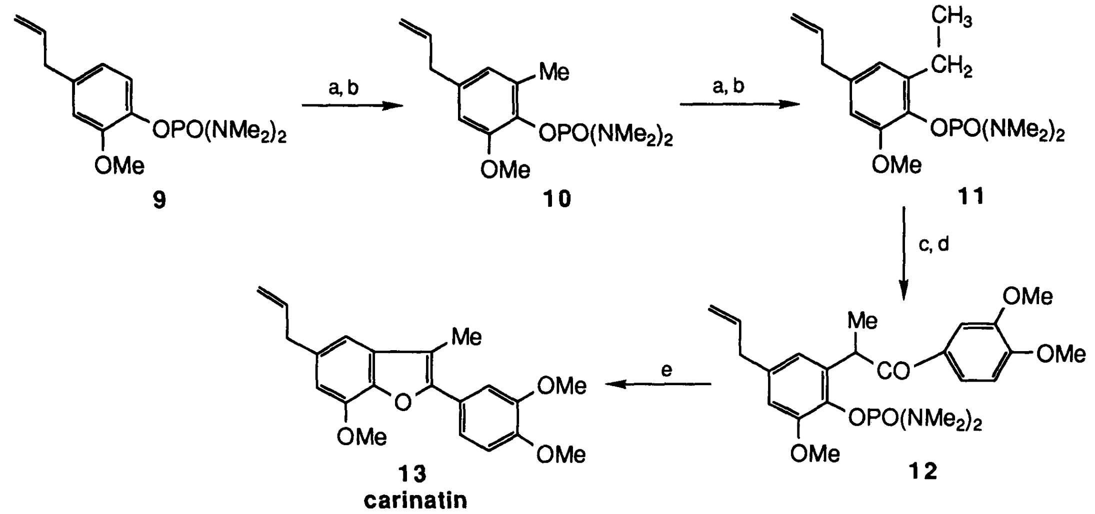
Chart 3

Table I. Synthesis of Deoxybenzoin Derivatives (7) and 2-Arylbenzofurans (8)

Run	4	6	Deoxybenzoin (7)					Benzofuran (8)		
				R	Ar	Yield(%)	mp (°C)		Yield(%)	mp (°C)
1	**4a**	**6a**	**7a**	H	C_6H_5	74	105-106	**8a**	60	118-119[a]
2	**4a**	**6b**	**7b**	H	4-(MeO)-C_6H_4	60	77-78	**8b**	30	145-146[b]
3	**4a**	**6c**	**7c**	H	3,4-(MeO)$_2$-C_6H_3	79	114-115	**8c**	74	116-118[c]
4	**4b**	**6b**	**7d**	6-MeO	4-(MeO)-C_6H_4	70	148-150	**8d**	98	74-77
5	**4c**	**6a**	**7e**	3-MeO	C_6H_5	67	oil	**8e**	75	56-58
6	**4d**	**6a**	**7f**	4-MeO	C_6H_5	71	124-126	**8f**	85	121-123[d]

a) Lit. mp 119-120°C in D. R. Buckle and C. T. M. Rockell, J. Chem. Soc., Perkin Trans. 1, **1985**, 2443. b) Lit. mp 153-155°C in A. Herconet and M. LeCorre, Tetrahedron, 37, 2867 (1981). c) Lit. mp 124-126°C in J. Grimshaw and N. Thompson, J. Chem. Soc., Chem. Commun., **1987**, 240. d) Lit. mp 127°C in 5g).

the procedures *via* the formation of 2'-hydroxydeoxybenzoin derivatives as a key step are effective routes.[3,5] As shown in Chart 3, when **4a** was lithiated and subsequently treated with methyl benzoate (**6a**), deoxybenzoin derivative **7a** was obtained in 74% yield. Acidic treatment of **7a** in refluxing formic acid[2] for 1 h gave 2-phenylbenzofuran (**8a**) in 60% yield. Methoxy-substituted 2-arylbenzofurans (**8b-f**) were synthesized in a similar manner starting from methoxy-substituted phosphates (**4b-d**) and benzoates (**6a-c**) in two steps (Table I). Since **4b-d** are easily and regioselectively accessible by the directed lithiation of the corresponding phosphates followed by methylation,[2] the above sequences provide a general and efficient route to 2-arylbenzofuran derivatives.



a *sec*-BuLi/THF/-105°C ; b MeI/-105°C ; c *sec*-BuLi/TMEDA/THF/-105°C
d **6c**/-105°C ; e HCOOH/reflux

Chart 4

The utility of the above benzofuran synthesis was demonstrated for the total synthesis of the neolignan, carinatin. Carinatin is a 2-arylbenzofuran natural product isolated from the bark of *Virola carinata* (Benth.) Warburg in 1982 and is identified as 5-allyl-7-methoxy-3-methyl-2-(3',4'-dimethoxyphenyl)benzofuran.$^{4)}$ *O*-Bis(dimethylamino)phosphorylated eugenol (**9**) was lithiated with *sec*-BuLi at -105 °C followed by treatment with MeI to give **10** in 96% yield. Compound **10** was lithiated and subsequently methylated to afford ethyl compound **11** in 96% yield. Compound **11** was also prepared in 95% yield, without isolation of **10**, in a tandem manner$^{6)}$ starting from **9**. Lithiation of **11** with *sec*-BuLi in the presence of TMEDA at -105 °C gave, after treatment with methyl 3,4-dimethoxybenzoate (**6c**), compound **12** in 44% yield. Acidic treatment of **12** furnished **13** (mp 88-89 °C) in 64% yield (Chart 4). The synthetic **13** thus obtained was shown to be identical with an authentic sample$^{4)}$ of carinatin on the basis of melting point (lit.$^{4)}$ mp 88-91 °C) and spectroscopic and thin-layer chromatographic comparisons.

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