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Aryllead triacetates in the synthesis of oxaphenanthrene derivatives

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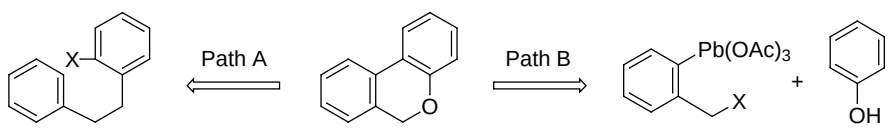
Abstract—*ortho*-Halomethylphenyllead triacetates (halo = bromine or chlorine) react with phenols in the presence of triethylamine and a pyridine derivative to afford modest to good yields of dibenzo[*b*,*d*]-6*H*-pyrans.

The dibenzo[*b*,*d*]pyran skeleton is present in a number of natural products,[1] as well as in apomorphine-derived σ ligands[2] or in progesterone receptor modulators.[3] Among the various strategies developed for their synthesis,[4–8] recent ones rely on an intramolecular palladium-catalyzed arylation reaction[7] or an intramolecular radical cyclization[8] (Path A, Scheme 1). A potentially attractive alternative would be a one-pot organolead-mediated *ortho*-arylation–cyclization sequence (Path B, Scheme 1).

The selective *ortho*-arylation of phenols by ligand coupling reaction with aryllead triacetates is now well documented.[9] This reaction is particularly useful for the introduction of electron-rich aryl groups which are frequently observed in natural products.[10] However, 2,6-diarylation is generally favoured even if, with a proper choice of conditions, moderate yields of the mono-arylation products can be obtained. If a second electrophilic centre is present in the aryllead reagent in a suitable geometric position, cyclization can be expected after the first arylation, thus avoiding the diarylation. But such a sequence requires that the lead centre is the most reactive one of the two electrophilic centres. For the synthesis of oxaphenanthrenes, an *ortho*-halomethylphenyllead triacetate is needed whereas the range of known aryllead triacetates is limited to polymethoxy- or polymethyl-phenyl derivatives. In view of the reactions of arylmagnesium reagents bearing an *ortho*-chloromethyl group recently reported by Cahiez and Knochel,[11] we considered the synthesis of organolead reagents **4** or **7** as possible (Scheme 2). Indeed, organolead reagents **4** or **7** can easily be prepared from the corresponding arylboronic acids **3** or **6**. The bromomethyl compound **3** was prepared from *ortho*-tolylboronic acid by dibenzoyl peroxide catalyzed bromination with *N*-bromosuccinimide in CCl_4 in 60% yield.[12] The chloro analogue **6** was not obtained when *N*-chlorosuccinimide was used as the source of halogen. However, reaction of 2-chloromethylphenylmagnesium bromide (prepared from 2-chloromethylphenyl iodide and isopropylmagnesium bromide)[11] with boron tris-isopropoxide afforded the boronic compound **6** in 52% yield. Transmetallation was performed by reaction of acids **3** or **6** with lead tetraacetate in the presence of mercuric acetate, according to Pinhey's procedure.[13] In this way, the air stable bromo compound **4** was isolated in 48% yield, and the air sensitive chloro compound **7** in 78% yield.



Scheme 1.

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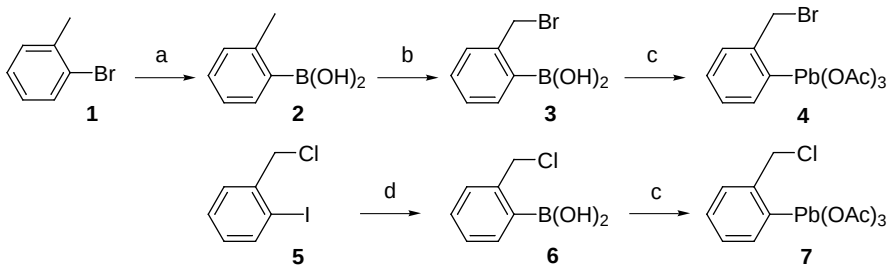


Scheme 2. (a) BuLi/B(O*i*-Pr)$_3$; (b) dibenzoylperoxide/*N*-bromosuccinimide/CCl_4; (c) $Pb(OAc)_4/Hg(OAc)_2$; (d) *i*-PrMgBr/B(O*i*-Pr)$_3$.

Using the classical procedure for phenol arylation with aryllead triacetates [phenol **8** or **10**, aryllead triacetate **4** (1.1 equiv.), pyridine (3 equiv.) at 45°C in $CHCl_3$], the oxaphenanthrene derivatives **9** or **11** were obtained directly, although in poor yields (20–25%). Pyridine plays a determinant, if not completely understood, role as a ligand in the lead atom sphere during the ligand coupling process leading to the formation of the *ortho*-arylphenol.[14] In the present system, the arylation step is followed by an intramolecular cyclization. The bromhydric acid which is liberated can abstract pyridine molecules from acting as ligand of the aryllead reagent. This could explain the low yields obtained under these conditions. However, increasing the amount of pyridine to 6 equivalents did not improve the yield. A second possibility is that pyridinium hydrobromide could react with the postulated (aryloxy)lead intermediate. The reaction of phenol **8** with the lead reagent **4** in the presence of a stronger base, TMG (*N*,*N*,*N*′,*N*′-tetramethylguanidine) (3 equiv.), did not afford any significant amount of the product **9**. However, when a second stronger base was added to pyridine, significantly improved yields were then observed (Table 1, entries 3 and 4). These observations further demonstrated the importance of pyridine or the related DMAP (4-dimethylaminopyridine) as a specific ligand in arylation reactions with aryllead triacetates. As aryllead reagents generated by boron–lead metal exchange can be advantageously used directly in the arylation reaction, we generally treated the crude reagent **4** or **7** with the phenolic substrates.

Moderate to relatively good overall yields were then obtained with other electron-rich phenols, and a modest yield was obtained in the reaction with a cyclic β-ketoester, the 4-hydroxycoumarin derivative **18**. It is interesting to note that even the hindered 3,5-di-*tert*-butylphenol **16** afforded the tricyclic compound **17** although in a modest yield (13%) (Table 1).

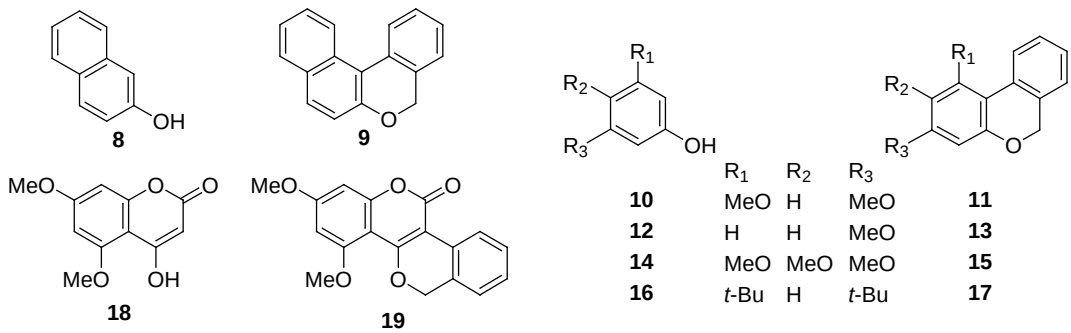


Table 1. Arylation–cyclization with aryllead reagent **4**[a]

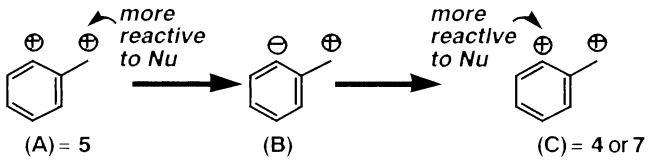
Entry	Substrate	**4**	Conditions	Products	Yield %
1	**8**	1.1 equiv.[b]	Pyridine (4 equiv.), 45°C, 10 h	**9**	25
2	**8**	1.1 equiv.[c]	Pyridine (4 equiv.), 45°C, 10 h	**9**	20
3	**8**	1.4 equiv.[c]	Pyridine (3 equiv.), Et_3N (3 equiv.), rt, 1 h	**9**	55
4	**8**	1.4 equiv.[c]	DMAP (3 equiv.), Et_3N (3 equiv.), rt, 1 h	**9**	65
5	**10**	1.1 equiv.[b]	Pyridine (5 equiv.), 50°C, 5 h	**11**	27
6	**10**	1.4 equiv.[c]	DMAP (3 equiv.), Et_3N (3 equiv.), rt, 1 h	**11**	60
7	**12**	1.4 equiv.[c]	DMAP (3 equiv.), Et_3N (3 equiv.), rt, 4 h	**13**	38
8	**14**	1.4 equiv.[c]	Pyridine (3 equiv.), Et_3N (3 equiv.), rt, 10 h	**15**	37
9	**16**	1.4 equiv.[c]	Pyridine (3 equiv.), Et_3N (3 equiv.), rt, 10 h	**17**	13
10	**18**	1.4 equiv.[c]	Pyridine (3 equiv.), Et_3N (3 equiv.), rt, 5 h	**19**	25

[a] The reactions were performed in $CHCl_3$ (5 cm^3/mmol of substrate); DMAP = 4-dimethylaminopyridine.
[b] Pure isolated **4** was used.
[c] In situ generated **4** was used.

Table 2. Arylation–cyclization with aryllead reagent **7**[a]

Substrate	**8**	**10**	**12**	**14**	**16**	**18**
Conditions	rt, 10 h[b]	50°C, 10 h[b]	50°C, 6 h[b]	50°C, 10 h[c]	50°C, 10 h[c]	50°C, 6 h[c]
Products	**9**	**11**	**13**	**15**	**17**	**19**
Yield (%)	55	42	33	26	6	21

[a] The reactions were performed with in situ generated **7** (1.4 equiv.), pyridine or DMAP (3 equiv.), Et_3N (3 equiv.) in $CHCl_3$ (5 cm^3/mmol of substrate).
[b] DMAP (4-dimethylaminopyridine) was used as the coordinating base.
[c] Pyridine was used as the coordinating base.



Scheme 3.

When the same system (phenol, aryllead triacetate and two bases) was applied to the chloromethylphenyllead reagent **7**, slightly lower yields were obtained in all cases and the reactions were more sluggish, requiring longer reaction times and/or higher temperatures (50°C) (Table 2).

In conclusion, functional group interconversion of a dicationic equivalent (A) possessing a more reactive benzylic centre can be transformed, via a zwitterion (B), into a second dicationic equivalent (C) in which the aromatic electrophilic centre is more reactive towards nucleophilic reagents than the benzylic centre (Scheme 3). Indeed, 2-halomethylphenylboronic acids can be easily transmetallated with lead tetraacetate to afford the 2-halomethylphenyllead triacetates **4** or **7**, in which the presence of the halogen atom in the coordinating sphere of the lead atom does not significantly alter the usual reactivity of aryllead triacetates towards soft nucleophiles.

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