Use of 2-(methoxycarbonyl)phenyllead triacetate in lactone synthesis

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Reactions of 2-(methoxycarbonyl)phenyllead triacetate with β-oxo lactones and phenols in the presence of pyridine afforded polycyclic lactones in good yields. A one-pot three-step synthesis without isolation of intermediate products was developed.

Key words: lactones, isocoumarins, organolead compounds, arylboronic acids, α-arylation, reductive cross-coupling.

Aryllead triacetates are widely used as *C*- and *N*-arylating reagents for organic compounds of various classes.[1] One of the most striking examples of the efficiency of such reagents is the high-yielding arylation of natural flavonoids and their analogs. A variety of the resulting flavone derivatives include isoflavones, isoflavonones,[2] 3-hydroxyneoflavonoids,[3] and 3-aryl-4-hydroxycoumarins (Scheme 1, pathway *A*).[4] Later, we have found that the use of polyfunctional aryllead triacetates containing two electrophilic centers allows the cascade synthesis of substituted benzopyrano-[5] and isoquinolinocoumarins[6] (Scheme 1, pathways *B* and *C*), where three to four successive steps are carried out without isolation of intermediate products.

The goal of the present work was to develop a novel cascade methodology for the creation of lactone systems of the type **A** from enolizable substrates (*e.g.*, those having the 4-hydroxycoumarin moiety) with the use of arylating organolead reagents (see Scheme 1, pathway *D*). Only a few studies[7,8] have been devoted to the synthesis of derivatives of the type **A**. For instance, these compounds have been obtained by the Pechmann condensation of 4-hydroxycoumarins with ethyl 2-oxocyclohexanecarboxylate followed by catalytic dehydrogenation of the cyclohexane ring.[7] Alternatively, reactions of 4-hydroxycoumarins with 2-bromobenzoic acid in the presence of $CuSO_4$ [8] or with methyl salicylate in the presence of a base have been used. However, these methods are ineffective for the synthesis of isocoumarins of the type **A** from electron-enriched polymethoxycoumarins. Interest in this class of compounds is due to unique photo- and electrooptical properties that could be exhibited by polymethoxy- and/or polyhydroxyisocoumarins **A** with a powerful closed π-system.[9] In addition, tetracyclic isostructural analogs of dilactone **A** (natural benzopyrano-, benzofurano-, isoquinolino-, and indolocoumarins) show a broad spectrum of useful biological properties such as antitumor,[10] antiviral (including anti-HIV-1),[11] antiinflammatory, and anticoagulating activities;[12] some of them are promising agents for treatment of neurodegenerative diseases, *e.g.*, Alzheimer disease.[13]

The synthesis of isocoumarins **A** with the use of organolead reagents implies a sequence of three "one-pot" steps (Scheme 2). Transmetalation between arylboronic acid **1** and lead tetraacetate in the presence of catalytic amounts of mercury diacetate gives 2-(methoxycarbonyl)phenyllead triacetate (**2**).[14] We failed to isolate reagent **2** in the individual state and used it in subsequent syntheses as solutions. Supposedly, *C*-arylation of enolizable substrates with participation of aryllead triacetates proceeds through the formation of covalent intermediate **3**,[15] its decomposition to α-arylation product **4**, and fi-

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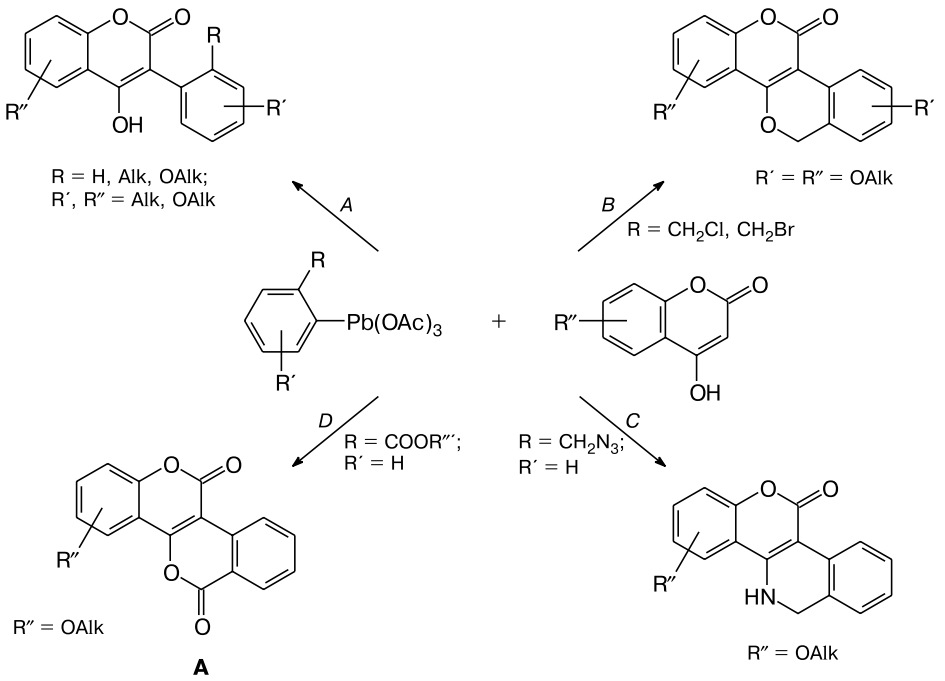
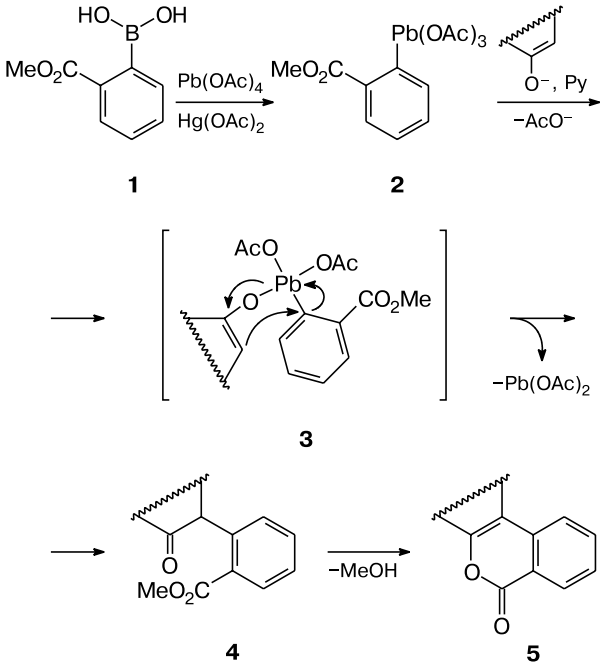
Scheme 1

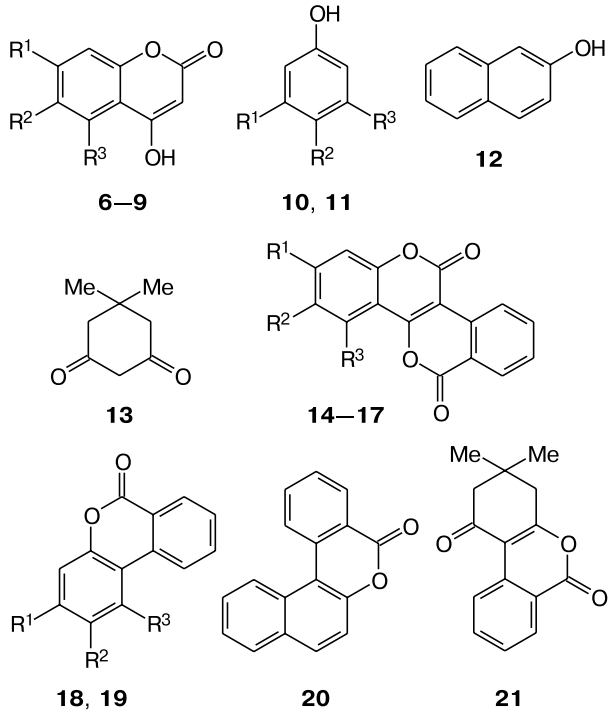


nally the spontaneous transesterification with the enolized oxo group, yielding annulation product **5**.

Scheme 2



The reactivity of reagent **2** was tested in reactions with the following substrates: unsubstituted 4-hydroxycoumarin (**6**), its natural dimethoxy and trimethoxy analogs **7**—**9**, 3,5-dimethoxy- (**10**) and 3,4,5-trimethoxyphenols (**11**), 2-naphthol (**12**), and β-diketone **13**.



Compound	R^1	R^2	R^3
6, **14**	H	H	H
7, **10**, **15**, **18**	OMe	H	OMe
8, **16**	OMe	OMe	H
9, **11**, **17**, **19**	OMe	OMe	OMe

Reactions of 4-hydroxycoumarins **6**—**9** with lead reagent **2** under classic conditions[14] in the presence of pyridine (3 equivalents with respect to compound **2**) gave isocoumarins **14**—**17** in 45, 42, 30, and 56% yields, respectively. Earlier,[5a,b,16] it has been demonstrated that the nature of the base employed in the *C*-arylation with organolead reagents can largely affect the reaction kinetics and the yields of the arylation products. Presumably,[1] covalent reaction intermediate **3** can contain one or two molecules of the base or the complexing agent, the nature of which substantially influences the topological conformational transformations in the coordination sphere of the heteroatom and the solubility of polar organolead intermediate **3**. For this reason, to optimize the yields of target products in reactions of reagent **2** with coumarins **6**—**9**, we used, apart from pyridine, a number of other bases: *o*-phenanthroline (3 equivalents with respect to compound **2**), pyridine—Et_3N (3 equiv. each), pyridine—*o*-phenanthroline (3 equiv. each), and *o*-phenanthroline—Bu^tOK (3 and 1 equiv., respectively). It was found that the yields of target products **14**—**17** did not increase in the presence of the above systems of bases. In contrast, reactions of 2-(bromomethyl)aryllead triacetates with analogous organic substrates afforded good yields of annulated benzopyranocoumarins.[5b,c]

The arylation of 3,5-dimethoxy- (**10**) and 3,4,5-trimethoxyphenols (**11**) gave lactones **18** and **19** in 41 and 29% yields, respectively. The arylation of 2-naphthol (**12**), which usually reacts well with organolead reagents, afforded compound **20** in 38% yield. With β-diketone **13** as a substrate, annulation product **21** was not obtained.

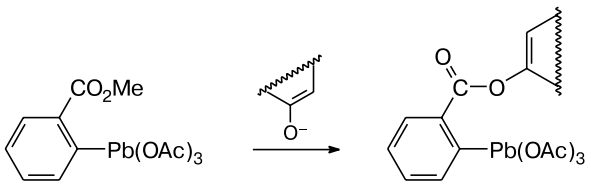
It should be noted that the arylation of 4-hydroxycoumarins **6**—**9** and phenols **10**—**12** with reagent **2** gave only the corresponding lactones **14**—**20**. The final reaction mixture contained trace amounts of the nonconsumed substrates, while α-arylation products of the type **4** were never detected. This fact suggests that the step **4** → **5** is much faster than the step **3** → **4**. The nonquantitative yield of the target products is probably due to parallel side processes.

A reaction that can compete with α-arylation proceeding through the formation of intermediate **3** may be an intermolecular transesterification[17] between substrates **6**—**12** and reagent **2** (Scheme 3). In this case, the substrate molecule incorporated in the ester fragment loses the nucleophilic center required for an attack on the lead atom in reagent **2**. Attempted isolation of organolead derivative **22** in the individual state was as unsuccessful as with compound **2**. The reactions of reagent **2** with 2-naphthol (**12**) and 4-hydroxycoumarins **6** and **8** were followed by acid hydrolysis giving rise to complex mixtures of organic products from which we failed to isolate acids formed upon the protolysis of intermediate **22**.

In conclusion, note that arylating reagents based on aryl derivatives of lead, bismuth, boron, iodine, and sulfur have found new synthetic applications in the post-Ullmann chemistry in the last decade.[1,2,18] Here we showed for the first time that polyfunctional derivatives of this series are suitable for the cascade-type synthesis of lactones from enolizable substrates and phenols. Moderate yields of the target products (29—56%) correlate with common total yields of three successive steps of the lactone synthesis without isolation of intermediates, which undoubtedly makes the advanced approach more valuable.

Further investigations will be aimed at optimizing the yields of the target products and searching for more efficient arylating reagents.

Scheme 3



2 **22**

Experimental

NMR spectra were recorded on a Bruker AC-200 spectrometer (200.13 (^{1}H) and 50.32 MHz (^{13}C)) in $CDCl_3$. Chemical shifts are given on the δ scale with reference to Me_4Si. 4-Hydroxycoumarin derivatives **6**—**9** were prepared according to known procedures.[4a,c,19] Commercial $Hg(OAc)_2$, 2-(methoxycarbonyl)phenylboronic acid, dimedone (**13**), and *o*-phenanthroline (Lancaster) were used as purchased.

6*H*,11*H*-[2]Benzopyrano[4,3-*c*][1]benzopyran-6,11-dione (14). A mixture of lead tetraacetate (0.123 g, 0.28 mmol), mercury diacetate (0.009 g, 0.028 mmol), and 2-(methoxycarbonyl)phenylboronic acid (**1**) (0.05 g, 0.28 mmol) in freshly distilled $CHCl_3$ (1 mL) was stirred at 45 °C for 1.5 h and then at ~20 °C for 12 h. 4-Hydroxycoumarin (**6**) (0.041 g, 0.2502 mmol) and pyridine (0.066 g, 0.833 mmol) were added and the resulting solution was stirred at 60—65 °C for 15 h. After the reaction was completed, volatile compounds were removed under reduced pressure and the residue was purified by column chromatography on SiO_2 with AcOEt—light petroleum (3 : 7) as an eluent. The yield of product **14** was 0.030 g (45%), colorless crystals, m.p. 190 °C. Found (%): C, 72.67; H, 3.11. $C_{16}H_8O_4$. Calculated (%): C, 72.73; H, 3.05. ^{1}H NMR, δ: 7.41—7.65 (m, 4 H, H(2), H(3), H(4), H(8)); 7.92 (t, 1 H, H(9), J = 7.2 Hz); 8.18 (d, 1 H, H(1), J = 7.2 Hz); 8.41 (d, 1 H, H(10), J = 7.6 Hz); 9.20 (d, 1 H, H(7), J = 8.2 Hz). ^{13}C NMR, δ: 113.4, 116.8, 120.3, 123.6, 125.0, 129.5, 133.1, 133.7 (CH); 101.1, 126.5, 130.2, 136.2, 152.5, 157.7, 159.0, 159.1 (quaternary C atoms).

Other lactones were obtained analogously.

2,4-Dimethoxy-6*H*,11*H*-[2]benzopyrano[4,3-*c*][1]benzopyran-6,11-dione (15). The yield was 42%, colorless crystals decomposing at 200 °C. Found (%): C, 66.74; H, 3.90. $C_{18}H_{12}O_6$. Calculated (%): C, 66.67; H, 3.73. ^{1}H NMR, δ: 3.90, 4.02 (both s, 3 H each, OMe); 6.41 (d, 1 H, H(3), J = 2.2 Hz); 6.52 (d, 1 H, H(1), J = 2.2 Hz); 7.58 (t, 1 H, H(8) or H(9),

J = 7.5 Hz); 7.87 (td, 1 H, H(8) or H(9), J_1 = 7.9 Hz, J_2 = 1.5 Hz); 8.37 (d, 1 H, H(10), J = 7.8 Hz); 9.17 (d, 1 H, H(7), J = 8.4 Hz). ^{13}C NMR, δ: 55.9, 56.6 (OMe); 93.0, 96.4, 126.0, 128.4, 129.8, 135.8 (CH); 98.0, 98.4, 119.3, 133.9, 156.0, 159.2, 159.3, 159.5, 160.4, 164.6 (quaternary C atoms).

2,3-Dimethoxy-6*H*,11*H*-[2]benzopyrano[4,3-*c*][1]benzopyran-6,11-dione (16). The yield was 30%, colorless crystals decomposing at 220 °C. Found (%): C, 66.51; H, 3.86. $C_{18}H_{12}O_6$. Calculated (%): C, 66.67; H, 3.73. ^{1}H NMR, δ: 3.97, 4.02 (both s, 3 H each, OMe); 6.90 (s, 1 H, H(4)); 7.45 (s, 1 H, H(1)); 7.61 (t, 1 H, H(8) or H(9), J = 7.5 Hz); 7.90 (t, 1 H, H(8) or H(9), J = 7.6 Hz); 8.39 (d, 1 H, H(10), J = 8.1 Hz); 9.17 (d, 1 H, H(7), J = 8.2 Hz). ^{13}C NMR, δ: 56.5, 56.6 (OMe); 99.6, 103.0, 126.1, 128.8, 130.1, 136.1 (CH); 98.9, 105.5, 119.7, 133.7, 147.1, 149.0, 154.7, 158.0, 159.4, 159.5 (quaternary C atoms).

2,3,4-Trimethoxy-6*H*,11*H*-[2]benzopyrano[4,3-*c*][1]benzopyran-6,11-dione (17). The yield was 56%, colorless crystals, m.p. 220 °C. Found (%): C, 64.52; H, 3.86. $C_{19}H_{14}O_7$. Calculated (%): C, 64.41; H, 3.98. ^{1}H NMR, δ: 3.92, 3.97, 4.10 (all s, 3 H each, OMe); 6.74 (s, 1 H, H(1)); 7.61 (td, 1 H, H(8) or H(9), J_1 = 7.5 Hz, J_2 = 1.0 Hz); 7.88 (td, 1 H, H(8) or H(9), J_1 = 7.8 Hz, J_2 = 1.5 Hz); 8.39 (dd, 1 H, H(10), J_1 = 7.8 Hz, J_2 = 1.2 Hz); 9.19 (d, 1 H, H(7), J = 8.2 Hz). ^{13}C NMR, δ: 56.5, 61.4, 62.3 (OMe); 96.1, 119.6, 126.2, 133.6, 135.9 (CH); 98.8, 101.8, 128.8, 129.9, 140.8, 150.5, 151.4, 158.3, 158.9, 159.1, 159.3 (quaternary C atoms).

1,3-Dimethoxy-6*H*-benzo[*c*]chromen-6-one (18). The yield was 41%, brown crystals, m.p. 180 °C. Found (%): C, 70.37; H, 4.64. $C_{15}H_{12}O_4$. Calculated (%): C, 70.31; H, 4.72. ^{1}H NMR, δ: 3.88, 4.02 (both s, 3 H each, OMe); 6.45 (s, 1 H, H(2)); 6.54 (s, 1 H, H(4)); 7.47 (t, 1 H, H(8) or H(9), J = 6.6 Hz); 7.75 (t, 1 H, H(8) or H(9), J = 7.0 Hz); 8.39 (d, 1 H, H(10), J = 7.0 Hz); 8.88 (d, 1 H, H(7), J = 8.0 Hz). ^{13}C NMR, δ: 55.8, 56.0 (OMe); 94.1, 95.9, 126.3, 126.9, 130.1, 134.7 (CH); 102.0, 119.7, 135.0, 153.7, 159.7, 161.0, 161.9 (quaternary C atoms).

1,2,3-Trimethoxy-6*H*-benzo[*c*]chromen-6-one (19). The yield was 29%, colorless crystals, m.p. 107 °C. Found (%): C, 67.32; H, 5.08. $C_{16}H_{14}O_5$. Calculated (%): C, 67.13; H, 4.93. ^{1}H NMR, δ: 3.91, 3.93, 4.01 (all s, 3 H each, OMe); 6.72 (s, 1 H, H(4)); 7.47—7.55 (m, 1 H, H(8) or H(9)); 7.79 (td, 1 H, H(8) or H(9), J_1 = 7.8 Hz, J_2 = 1.4 Hz); 8.40 (dd, 1 H, H(10), J_1 = 8.0 Hz, J_2 = 1.2 Hz); 8.87 (d, 1 H, H(7), J = 8.0 Hz). ^{13}C NMR, δ: 56.1, 60.6, 61.2 (OMe); 96.9, 125.5, 127.6, 130.3, 135.1 (CH); 105.5, 120.0, 134.7, 139.8, 148.3, 152.2, 154.6, 161.4 (quaternary C atoms).

5*H*-Benzo[*d*]naphtho[2,1-*b*]pyran-5-one (20). The yield was 38%, yellow crystals, m.p. 155 °C. Found (%): C, 83.09; H, 4.26. $C_{17}H_{10}O_2$. Calculated (%): C, 82.91; H, 4.09. ^{1}H NMR, δ: 7.47—7.68 (m, 4 H, H(3), H(11), H(10), H(7)); 7.90—7.97 (m, 3 H, H(8), H(2), H(12)); 8.51 (dd, 1 H, H(9), J_1 = 7.8 Hz, J_2 = 1.1 Hz); 8.66 (d, 1 H, H(1), J = 8.2 Hz); 8.78 (d, 1 H, H(4), J = 8.4 Hz). ^{13}C NMR, δ: 117.6, 122.3, 125.0, 125.4, 126.4, 127.8, 128.2, 129.3, 131.5, 134.3 (CH); 112.6, 129.5, 130.7, 131.6, 135.4, 150.3, 161.3 (quaternary C atoms).

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