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A FACILE SYNTHESIS OF 3-ARYL-4-HYDROXYCOUMARINS

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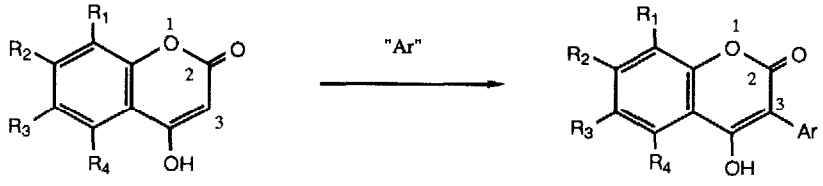
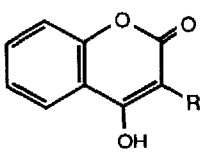
Abstract A range of 3-aryl-4-hydroxycoumarins have been prepared by direct arylation of 4-hydroxycoumarin derivatives by variously substituted aryllead triacetates. Yields were temperature and substituent dependent.

The 3-aryl-4-hydroxycoumarins belong to the isoflavanoid class and are found mainly in the subfamily Papilionoideae (Leguminosae)[1]. To date thirteen examples have been identified from natural sources[2] and numerous synthetic analogues have been prepared[3]. 3-Aryl-4-hydroxycoumarins are also intermediates in the preparation of a second class of isoflavonoid, namely the coumestans[4,5,6]. The biological importance and considerable therapeutic potential of both of these isoflavonoid classes has generated considerable interest in efficient methodology for their synthesis. The simplest synthetic route to 3-aryl-4-hydroxycoumarins is direct arylation at C-3 of the preformed coumarin ring.

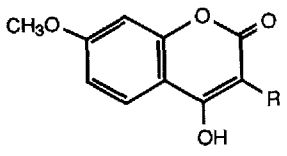


Direct coupling of 4-hydroxycoumarin with aryldiazonium chloride was reported[7] to give 3-aryl-4-hydroxycoumarins in low yields (12-22%). A major limitation of this method is that the reaction is inhibited when the diazonium chloride is *ortho*-substituted. Direct arylation with arylbismuth^{V} reagents was recently reported[8] to give 3-aryl-4-hydroxycoumarins in good yield. However, there is a limited availability of suitably substituted alkoxyphenylbismuth^{V} reagents due to difficulty in their preparation. Consequently, we decided to investigate the use of a second class of organometallic compounds, namely the aryllead^{IV} triacetates[9]. These, like the arylbismuth compounds[10,11], were shown to act as aryl cation equivalents which effect the arylation of carbon and other nucleophiles under mild conditions[11,12].

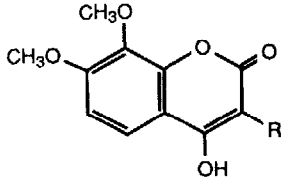
We now report our preliminary results on the preparation of a range of 3-aryl-4-hydroxycoumarins via C-3 arylation of substituted and unsubstituted 4-hydroxycoumarins by aryllead^{IV} triacetates (Table 1).



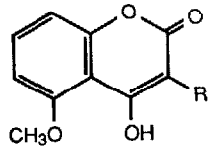
1 R = H
3 R = C_6H_5
5 R = 4-CH_3O C_6H_4
7 R = 2,4-$(CH_3O)_2$ C_6H_3
9 R = 2,4,6-$(CH_3O)_3$ C_6H_2



10 R = H
11 R = 4-CH_3O C_6H_4
12 R = 2,4-$(CH_3O)_2$ C_6H_3

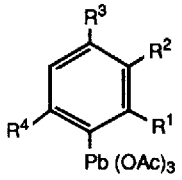


13 R = H
14 R = 4-CH_3O C_6H_4
15 R = 2,4,6-$(CH_3O)_3$ C_6H_2



16 R = H
17 R = 4-CH_3O C_6H_4
18 R = 2,4,6-$(CH_3O)_3$ C_6H_2
20 R = 3,4-$(CH_3O)_2$ C_6H_3
22 R = 3,4-(OCH_2O) C_6H_3
23 R = 2,4-$(CH_3O)_2$ C_6H_3

Two convenient routes exist for the preparation of alkoxyphenyllead triacetates with the oxygenation pattern required for the synthesis of B-ring substituted 3-aryl-4-hydroxycoumarins. Direct plumbylation of aromatics[13] was used to prepare aryllead triacetates **4**, **6** and **8**. Aryltributylstannane was treated with lead tetraacetate and a catalytic amount of mercuric acetate in chloroform[14] to prepare aryllead triacetates **19** and **21**. The substitution pattern of **21** is frequently observed in naturally occurring 3-aryl-4-hydroxycoumarins.



Aryllead Triacetate	R^1	R^2	R^3	R^4
2	H	H	H	H
4	H	H	OCH_3	H
6	OCH_3	H	OCH_3	H
8	OCH_3	H	OCH_3	OCH_3
19	H	OCH_3	OCH_3	H
21	H	$-OCH_2O-$		H

Pinhey *et al.* have shown[15] that aryllead triacetates react with β-diketones to give only diarylated products[13]. As the coumarin ring can tautomerise to the β-diketo form, diarylated products could occur. However, only monoarylated products were obtained because of the greater stability of the coumarin ring in the enolic form. The similarity in chemistry between arylbismuth^V and aryllead^{IV} triacetates is again observed as only monoarylated products were obtained when the former compounds were the arylating agents[10]. Moreover, the 4-hydroxyl behaves more like a phenolic hydroxyl and phenols were shown[16] to give mono-*ortho*-arylated products.

Table 1 Reaction of Arylleadtriacetates with 4-Hydroxycoumarins[a].

Entry	Substrate	Aryllead Triacetate	Temperature (°C)	Time (h)	Product (%)[b]
1	**1**	**2**	40	16	**3** (40)
2	**1**	**2**	60	16	**3** (49)
3	**1**	**4**	60	16	**5** (47)
4	**1**	**6**	60	16	**7** (95)
5	**1**	**8**	60	16	**9** (87)
6	**10**	**4**	60	16	**11** (44)
7	**10**	**6**	60	16	**12** (85)
8	**13**	**4**	60	16	**14** (59)
9	**13**	**8**	40	10	**15** (76)
10	**13**	**8**	60	6	**15** (94)
11	**16**	**4**	60	16	**17** (75)
12	**16**	**6**	60	16	**18** (95)
13	**16**	**19**	60	16	**20** (68)
14	**16**	**21**	60	16	**22** (60)
15	**16**	**8**	60	16	**23** (97)

a Reactions were carried out in dry chloroform (0.6 mmole per ml of solvent). The molar ratio of substrate : aryllead triacetate : pyridine was in all cases 1 : 1.1 : 3.3.

b Isolated yields are unoptimised.

The increase in temperature from 40°C to 60°C led to an increase in yield (entries 1, 2, 9 and 10) and the latter temperature was then used for all other experiments cited. Highest yields were obtained when the B-ring was *ortho*-substituted (entries 4, 5, 7, 9 and 10). When the B-ring was not *ortho*-substituted only moderate yields were obtained (entries 2, 3, 6 and 8).

However, when the 5-position is methoxylated, the enolic form is more stabilised thus favouring formation of the putative lead intermediate. The arylated products are formed in good to excellent yields (entries 11-15) regardless of the substitution in the B-ring.

Studies are currently underway on the synthesis of naturally occuring 3-aryl-4-hydroxycoumarins having highly functionalised A-rings and the results of these investigations will be reported in due course.

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