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SYNTHESIS OF 2-ARYL-3(2*H*)-BENZOFURANONES

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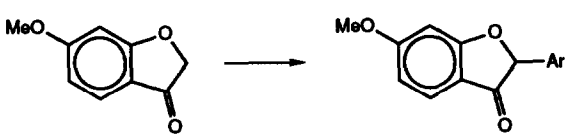
Abstract: A range of 2-aryl-6-methoxy-3(2*H*)-benzofuranones **26 - 32**, which are seen as precursors to 2-aryl-3(2*H*)-benzofurans, have been prepared by arylation of allyl β-ketoester **18** with aryllead(IV) reagents.

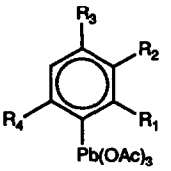
2-Aryl-(2*H*)-benzofurans have an extensive natural distribution and are believed to be formed in nature from three different biosynthetic sources [1]. 2-Aryl-(2*H*)-benzofurans isolated from *Styrax* and *Eupomatia* species are seen as having a bisarylpropanoid (lignan or neolignan) origin. The oxidative cyclisation of hydroxystilbenes is envisaged as the source of 2-aryl-(2*H*)-benzofurans found in *Morus* species. The Leguminosae contain several phytoalexin 2-aryl-(2*H*)-benzofurans and these seem to be related to isoflavanoids found in these plants. The chemical synthesis of 2-aryl-(2*H*)-benzofurans is well documented [2, 3] but of those reported only one, incorporating copper (I) acetylide substitution [4], can be said to be in any way a general synthesis [5, 6]. The main disadvantage of the reported syntheses is the low yield of the product.

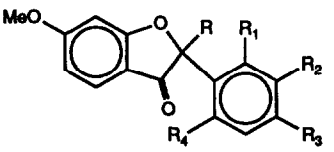
We envisage a general synthesis of 2-aryl-(2*H*)-benzofurans by the reduction and subsequent dehydration of 2-aryl-3(2*H*)-benzofuranones. We herein report our preliminary results on the preparation of 2-aryl-6-methoxy-3(2*H*)-benzofuranones starting with 6-methoxy-3(2*H*)-benzofuranone (**1**). The key step is the direct insertion of the aryl group into the C-2 position of the benzofuranone using aryllead (IV) triacetates [7]. These, like arylbismuth (V) compounds [8, 9], act as aryl cation equivalents effecting substitution of hydrogen on nucleophiles [9, 10]. Recently we reported preliminary work on the synthesis of 3-aryl-4-hydroxycoumarins [11] and 4-arylcoumarins [12] using aryllead (IV) triacetates.



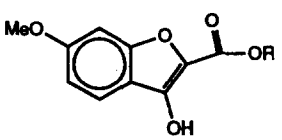
1 **26 - 32**

Two convenient routes exist for the preparation of aryllead (IV) triacetates. Aryllead (IV) triacetates **4**, **5**, **6**, and **8** were made by direct plumbylation [13] and aryllead (IV) triacetates **3** and **7** were prepared by a tin-lead exchange reaction [14].

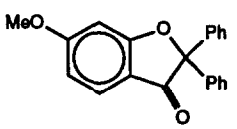




R^1	R^2	R^3	R^4	Aryllead Triacetate	Arylbenzofuranone R = CO_2Et	R = $CO_2CH_2CHCH_2$	R = H
H	H	H	H	2	10	19	26
OCH_3	H	H	H	3	11	20	27
H	H	OCH_3	H	4	12	21	28
H	H	CH_3	H	5	13	22	29
OCH_3	H	OCH_3	H	6	14	23	30
H	OCH_3	OCH_3	H	7	15	24	31
OCH_3	H	OCH_3	OCH_3	8	16	25	32



9: R = Et
18: R = Allyl



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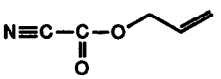

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Direct α-arylation of ketones with aryllead(IV) triacetates has not been reported. It requires activation of the ketone, as an enamine [15], a silyl enol ether [16] or a β-keto ester [17]. However, arylation of enamines is very sensitive to steric effects whilst silyl enol ethers undergo α-plumbylation under the reaction conditions employed. As β-keto esters are conveniently arylated with aryllead(IV) triacetates in high yields [17], 6-methoxy-3(2*H*)-benzofuranone **1** was converted to ethyl β-keto ester **9** in 71% yield using Mander's method [18] of generating β-keto esters from ketones. β-Keto ester **9** was reacted with a range of aryllead(IV) triacetates **2** - **8** to give the aryl-β-keto esters **10** - **16** in good to high yields (63 - 91%) (Table 1).

Table 1: Reactions of Aryllead(IV) Triacetates with β-ketoesters **9** and **18** [a].

β–Ketoester	9							18						
Aryllead(IV) Triacetate	2	3	4	5	6	7	8	2	3	4	5	6	7	8
Product	10	11	12	13	14	15	16	19	20	21	22	23	24	25
Yield % [b]	63	91	76	70	84	70	90	86	87	88	74	82	68	86

a Reactions were carried out in dry chloroform (0.6mmole per ml solvent) at 60°C for 5h. The molar ratio of substrate:aryllead triacetate:pyridine was in all cases 1:1.1:3.3.

b Isolated yields are unoptimised.

β-Keto esters are usually conveniently dealkoxycarbonylated and many methods exist [19] for achieving this transformation. However, the ethyl 2-aryl-β-keto esters prepared were resistant to all attempts at deethoxycarbonylation because of the steric hindrance of the substrate. As an alternative, we looked to the work of Tsuji on the palladium catalysed dealkyloxycarbonylation [20] of allyl β-keto esters. Allyl cyanoformate **17** was prepared from allyl chloroformate and potassium cyanide under phase-transfer catalysis [21] in 84% yield. Allyl cyanoformate **17** was reacted with ketone **1** to give β-keto ester **18** in 60% yield. The results of the reaction of β-keto ester **18** with aryllead (IV) triacetates are given in Table 1.

The 2-aryl-β-keto esters thus prepared were mildly deallyloxycarbonylated using catalytic amounts of palladium (II) acetate and triphenylphosphine in dry THF containing *in situ* formed triethylammonium formate under a nitrogen atmosphere at room temperature. Good yields of the 2-aryl-3(2*H*)-benzofuranones were obtained (67-88%). Our results are outlined in Table 2.

Table 2 Palladium Catalysed Deallyloxycarbonylation of 2-Aryl-β-keto allyl esters [a].

Entry	Substrate	Product (%) [b]
1	**19**	**26** (71)
2	**20**	**27** (80)
3	**21**	**28** (70)
4	**22**	**29** (67)
5	**23**	**30** (88)
6	**24**	**31** (75)
7	**25**	**32** (68)

a In all cases the reaction time was 3 days.

b Isolated yields are unoptimised.

A proposed mechanism for organolead arylation involves the formation of a covalent lead enolate followed by reductive elimination [22]. By analogy with the base-dependence in the arylation of enols and phenols with organobismuth reagents [23], we decided to investigate the effect of the strong N,N,N',N'-tetramethylguanidine (TMG) instead of the weaker pyridine, which is classically used in organolead arylations. Thus, reaction of **1** with phenyllead triacetate **2** (1.1 equiv.) and TMG (1 equiv.) gave a mixture of the 2,2-diphenyl derivative **33** (21%) and unreacted **1** (71%). However, use of 2.2 equivalents of **2** and TMG (2 equiv.) led to a high yield of **33** (84%). A complex mixture was observed in the reaction of **1** with organolead reagents **4** and **6**. Interestingly, the more sterically hindered **8** afforded the monoaryl derivative **32** although in a modest yield (31%). These results show that arylation of unactivated ketones can be effected by organolead reagents in the presence of a strong base. However, monoarylation of **1** cannot be obtained in high yield by such a reaction.

Acknowledgements

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