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Synthesis of 3-Arylbenzo[1,4]dioxin-2-carboxamides by Palladium-Catalysed Coupling of Vinylstannanes with Aryl Halides

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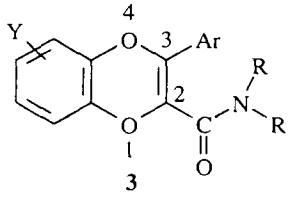
Abstract : Aryl iodides or bromides undergo a Pd (0)-CuI catalysed coupling with 3-(trialkylstannyl) benzo[1,4]dioxin-2-carboxamides to provide the corresponding 3-aryl derivatives.

The benzo[1,4]dioxins and 2,3-dihydrobenzo[1,4]dioxins form heterocyclic structures present in a lot of natural or synthetic derivatives which often exhibit interesting pharmacological profile[1,2]. Morever, it is to be noticed, that each series constitutes an ideal precursor of the other one[3].

In the course of our work on the synthesis of therapeutically valuable benzodioxinic compounds, we needed a general procedure allowing the preparation of carboxamides **3** bearing on position 3 various substituted aryl groups.



3

Y = H, OMe, O*i*Pr
R = Et, *i*Pr

The palladium-catalysed cross-coupling of organotin reagents with organic halides offers a method of C-C bond formation remarkable for its efficiency and selectivity[4], thus we decided to adopt this methodology for our purpose. We had previously reported that both benzo[1,4]dioxin-2-carboxylic acids and carboxamides were easily substituted on position 3 *via* the corresponding lithio derivatives[5], and we expected that the required vinyl stannanes **2** could be obtained in the same way (Scheme1). Indeed, when treated by lithium diisopropylamide

(2 eq, -78°C), compounds **1** led to the corresponding metallated heterocycles which reacted with the trimethyltin or tributyltin chlorides (2,5 eq) providing vinylstannanes **2** in high yields after hydrolysis and chromatographic purification (Table I).

Scheme **1**

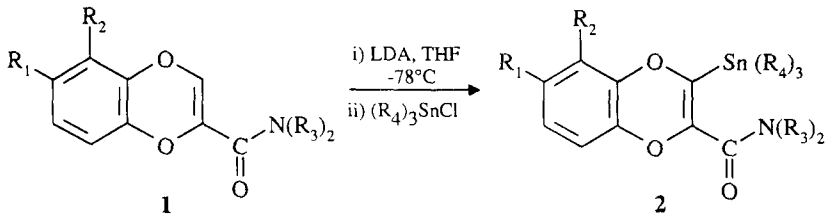


Table **I** : Reactions of 3-lithiobenzo[1,4]dioxin-2-carboxamides with trialkyltin chlorides.

2	R_1	R_2	R_3	R_4	yield (%) [a]
2a	H	H	Et	Me	94
2b	OMe	H	Et	Me	81
2c	O*i*Pr	H	Et	Me	89
2d	H	OMe	Et	Me	83
2e	H	H	Et	Bu	85
2f	H	H	*i*Pr	Bu	87

a) isolated yields

The vinylstanannes were then engaged in coupling reactions with various aryl iodides or bromides (Scheme **2**). The optimum conditions for the reaction were eventually obtained by using a freshly prepared tetrakis(triphenylphosphine)palladium (0) catalyst[6] in refluxing 1,4-dioxane, in the presence of copper(I) iodide[7]. Compounds **3** were obtained in acceptable yields (Table II); no significant disparity was observed between aryl iodides and bromides, neither between trimethyl- and tributylstannanes.

Scheme 2

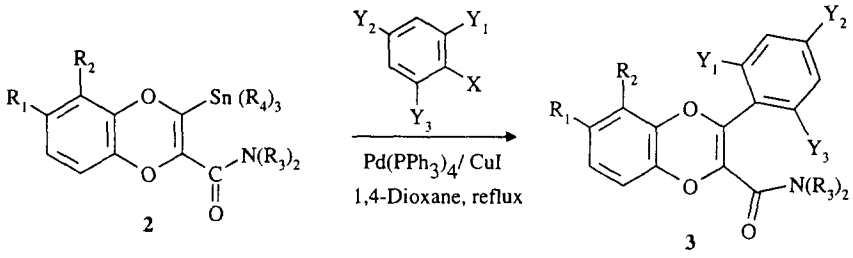


Table **II** : Cross-coupling reactions of benzodioxinic vinylstannanes with aryl halides.

Starting material	X	Y_1	Y_2	Y_3	**3** yield (%)[a]
2a	I	H	H	H	58[c]
2e	I	H	H	H	66[b]
2f	I	H	H	H	62[b]
2a	I	NHBoc	H	H	75[c]
2b	I	NHBoc	H	H	71[c]
2c	I	NHBoc	H	H	58[c]
2d	I	NHBoc	H	H	74[d]
2b	I	Me	H	H	67[b]
2c	I	Me	H	H	72[d]
2d	I	Me	H	H	61[d]
2e	Br	H	Me	H	73[b]
2f	Br	OMe	H	OMe	68[b]

a) isolated yields
b) 5 mol% Pd (0), 5 mol% CuI, 1eq of aryl halide
c) 5 mol% Pd (0), 10 mol% CuI, 1eq of aryl halide
d) 10 mol% Pd (0), 10 mol% CuI, 1eq of aryl halide

In conclusion we have developed an efficient synthesis of 3-arylbenzo[1,4]dioxin-2-carboxamides[8] *via* a palladium-catalysed coupling reaction involving heterocyclic vinylstannanes and aryl halides.

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8. All new compounds reported here have been fully characterised.

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