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Palladium catalysed arylation of 6,8-dimethoxybenzofuranone

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Abstract—6,8-Dimethoxybenzofuranone was arylated in the presence of a palladacycle catalyst and *p*-methoxyphenol to afford precursors of anti-cancer and anti-inflammatory drugs.

Rocaglamide **2** and its related flavaglines isolated from plants of the *Aglaia* species exhibit potent cytostatic and proapoptotic activity in cancer cells, but are not toxic to the organism.[1–3] Recent findings have shown that these compounds also display potent anti-inflammatory properties both in vitro and in vivo.[4,5] Their cellular target and mechanism of action are considered to be distinct from those of known anti-inflammatory and anti-cancer agents. The most straightforward syntheses of flavaglines start from **1** (Fig. 1).[6,7] However, these approaches suffer from the difficulty to prepare 2-arylbenzofuranones: the synthesis of these compounds by the Hoesch reaction is restricted to benzofuranones substituted by electron-donating groups.[8] Moreover, this reaction displays a lack of reproducibility as reported by Taylor and co-workers, and verified by us.[6]

In the course of our research on the structure–activity relationship of rocaglamide, we needed to develop a concise and flexible synthesis of 2-arylbenzofuranones. The recent development of palladium-catalysed α-arylation of ketones provides an opportunity to prepare these compounds.[9] To explore this reaction, we chose palladacycle **4** as a catalyst, due to its efficiency, stability and ease of preparation.[10]

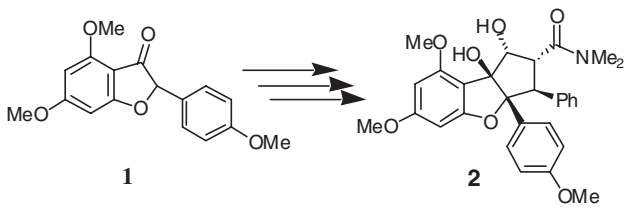

Figure 1. Rocaglamide **2** and its synthetic precursor **1**.

First, we examined the reaction of dimethoxybenzofuranone **3** with phenyl bromide in toluene under reflux. The use of K_3PO_4 as a base led exclusively to the formation of tar (Table 1, entry 1). Switching to a stronger base, *t*-BuOK, afforded the expected adduct **5** in low yield as well as O-phenyl ether **6** and diadduct **7** (entry 2).

Because the efficiency and the cleanliness of the reaction were poor, we examined whether the addition of *p*-methoxyphenol could improve this process as it has been observed by Buchwald with the arylation of enolates catalysed by $Pd_2(dba)_3$.[11] We were pleased to observe that this additive doubled the yield and suppressed totally the formation of diadduct **7** (entry 3). As far as we know, it is the first observation that a phenolate increases the efficiency of a palladacycle catalyst.

Increasing the quantity of phenylbromide to 2 equiv increased the yield up to 48% (entry 4). Only 10% of the by-product **6** was formed. Lowering the amount of *t*-BuOK to 2.5 equiv or replacing toluene by DMF decreased both the yield of arylation (entries 5 and 6).

As experience was gained with the previous example, we successfully applied the α-arylation reaction to several bromoarenes (Table 2).[12] Arylated benzofuranones were obtained in reasonable yields with a predominance of the desired adducts **8**.

Keywords: Arylation; Benzofuranone; Palladacycle.
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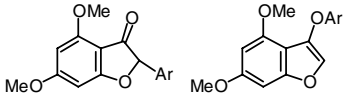
Table 1. α-Phenylation of benzofuranone **3**

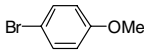
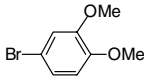
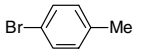
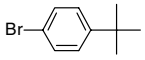
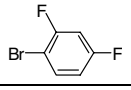
3 **4** (0.02 eq) (0 or 0.2 eq) **5** **6** **7**

Entry	PhBr (equiv)	Base (equiv)	Solvent	*p*-MeO-PhOH (equiv)	Isolated yield (%)		
					5	**6**	**7**
1	1	K_3PO_4 (1.5)	PhMe	0	0	0	0
2	1	*t*-BuOK (3)	PhMe	0	17	2	2
3	1.5	*t*-BuOK (3)	PhMe	0.2	41	13	0
4	2	*t*-BuOK (3)	PhMe	0.2	48	10	0
5	3	*t*-BuOK (2.5)	PhMe	0.2	32	6	0
6	2	*t*-BuOK (3)	DMF	0.2	33	5	0

Table 2. α-Arylation of **3** by various aryl bromides[a]



8 **9**

Entry	ArBr	Yield (%)	Ratio **8/9**
1		73	1.35/1
2		79	1.40/1
3		87	1.65/1
4		92	1.42/1
5		61	1.44/1

[a] All reactions were performed in toluene at 110 °C with 3 equiv of *t*-BuOK, 0.2 equiv of *p*-MeO-PhOH and 0.2 equiv of **4**.

In summary, the first α-arylation of benzofuranone has been developed to prepare building blocks for the synthesis of rocaglamide analogues. We have shown that *p*-methoxyphenol increases dramatically the efficiency of this reaction to afford a mixture of C- and O-arylated regioisomers.

References and notes

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11. Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168–15169.
12. Typical experimental procedure: A mixture of **3** (0.78 g, 4 mmol), 4-methoxyphenol (0.10 g, 0.8 mmol), *t*-BuOK (1.35 g, 12 mmol), bromoarene (12 mmol) and **4** (0.10 g, 0.8 mmol) was degassed for 2 min at rt under vacuum and stirred for 2 h at 110 °C under argon. After cooling at room temperature, the mixture was quenched with NH_4Cl and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, concentrated to dryness and purified by flash chromatography.