Oxygen Heterocycles

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Transition-Metal-Free Intramolecular Ullmann-Type O-Arylation: Synthesis of Chromone Derivatives**

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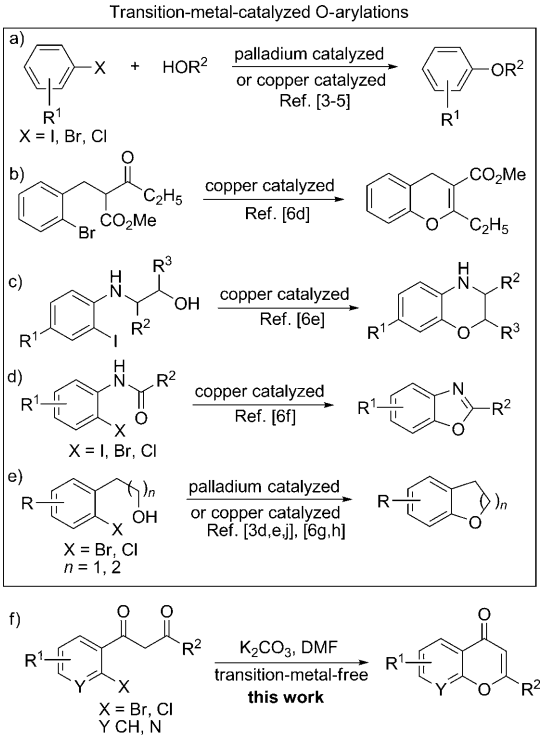
Aromatic C–O bond-forming reactions are important in organic synthesis because these bonds occur in numerous natural products, biological compounds, pharmaceuticals, fragrances, cosmetics, and polymers.[1] Traditionally, aryl ethers have been prepared by copper-mediated Ullmann coupling reactions of aryl bromides/iodides and phenols, but the drawbacks include harsh reaction conditions, such as: the need for a strong base, long reaction times in high polar solvents, and a stoichiometric amount of copper.[2] Subsequently, some significant achievements in the palladium-catalyzed O-arylation have been made under mild reaction conditions (Scheme 1a).[3] Recently, copper-catalyzed Ullmann-type O-arylations have been developed under milder reaction conditions (Scheme 1a) using inexpensive copper salts and readily accessible ligands,[4,5] such as phenanthrolines,[5j,5k] *N,N*-dimethyl glycine,[5l] pyridine derivatives,[5m] β-diketones,[5n] 1,1,1-tris(hydroxymethyl)ethane,[5o] and pyrrolidine-2-phosphonic acid phenyl monoester.[5p] Palladium- or copper-catalyzed intramolecular O-arylations have attracted much attention, and some oxygen heterocycles were constructed with the Ullmann-type O-arylation strategy,[6] for example copper-catalyzed synthesis of substituted 4*H*-1-benzopyrans (Scheme 1b),[6d] 2,3-dihydro-1,4-benzoxazines (Scheme 1c),[6e] benzoxazoles (Scheme 1d),[6f] and copper-[6g,h] and palladium-catalyzed[3d,e,j] synthesis of five and six-membered oxygen heterocycles (Scheme 1e). The results above show that transition-metal catalysts (palladium and copper) seem to be necessary in O-arylations.

Chromone derivatives are ubiquitous to green-plant cells and are highly diverse; more than 2000 different flavonoids have been identified, and their number is growing rapidly. These derivatives show various biological and pharmaceutical activity,[7] so they are interesting as structural scaffolds and have been assigned as privileged structures in drug development.[8] Although some approaches to the chromone derivatives have been developed, the methods often suffer from harsh reaction conditions, limited substrate scope, poor substituent tolerance, and low yields.[9] Several efficient palladium-catalyzed routes have been developed for the synthesis of chromone derivatives.[10] The excellent results from the copper- and palladium-catalyzed O-arylations above[1-6] prompted us to make chromone derivatives by using a transition-metal-catalyzed strategy. Thus, considering the ready availability and low toxicity of copper catalysts, we first screened copper-catalyzed reaction conditions by using the intramolecular O-arylation of 1-(2-bromophenyl)-3-*p*-tolylpropane-1,3-dione (**1a**) as the model reaction (Table 1). Surprisingly, a more highly efficient O-arylation was observed in the absence of a copper salt (entry 7, Table 1). Herein, we report the unexpected transition-metal-free intramolecular Ullmann-type O-arylation leading to chromone derivatives (Scheme 1f).



Scheme 1. a–e) Copper- and palladium-catalyzed Ullmann-type O-arylations (previous research). f) Transition-metal-free intramolecular Ullmann-type O-arylation leading to chromones (this work). DMF = *N*,*N*′-dimethylformamide.

1-(2-Bromophenyl)-3-*p*-tolylpropane-1,3-dione (**1a**) was first used as the model substrate to screen the reaction conditions for the optimization of the catalyst, base, solvent, temperature, and reaction time under air. As shown in Table 1, six copper catalysts were tested at 110 °C in the presence of one equivalent of Cs_2CO_3 (relative to the amount

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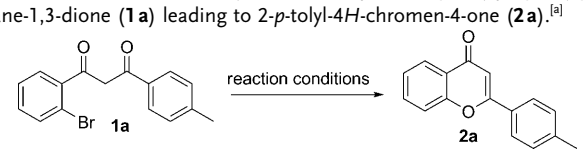
Table 1: Intramolecular O-arylation of 1-(2-bromophenyl)-3-*p*-tolylpropane-1,3-dione (**1a**) leading to 2-*p*-tolyl-4*H*-chromen-4-one (**2a**).[a]



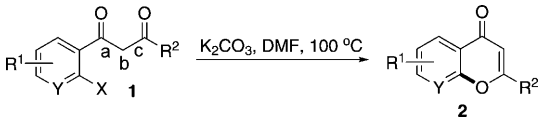
Entry	Cat.	Base	Solvent	T [°C]	t [h]	Yield [%][b]
1	CuI	Cs_2CO_3	DMF	110	12	26
2	CuBr	Cs_2CO_3	DMF	110	12	28
3	CuCl	Cs_2CO_3	DMF	110	12	30
4	Cu_2O	Cs_2CO_3	DMF	110	12	14
5	CuO	Cs_2CO_3	DMF	110	12	62
6	$Cu(OAc)_2$	Cs_2CO_3	DMF	110	12	64
7	–	Cs_2CO_3	DMF	100	1	96
8	–	Na_2CO_3	DMF	100	1	92
9	–	K_2CO_3	DMF	100	1	97
10	–	K_3PO_4	DMF	100	1	95
11	–	NaOH	DMF	100	8	62
12	–	NaH	DMF	100	7	75
13	–	–	DMF	100	8	8
14	–	K_2CO_3	DMSO	100	1	93
15	–	K_2CO_3	NMP	100	1	92
16	–	K_2CO_3	dioxane	100	24	trace
17	–	K_2CO_3	toluene	100	12	trace
18	–	K_2CO_3	EtOH	60	12	trace
19	–	K_2CO_3	H_2O	100	12	trace
20	–	K_2CO_3	DMF	80	6	90
21	–	K_2CO_3[c]	DMF	100	1	95

[a] Reaction conditions: 1-(2-bromophenyl)-3-*p*-tolylpropane-1,3-dione (**1a**) (0.5 mmol), catalyst (0.05 mmol), base (0.5 mmol), solvent (2 mL), under air. [b] Yield of isolated product. [c] Use of highly pure K_2CO_3 from Alfa Aesar company (99.997% purity). DMSO = dimethylsulfoxide, NMP = 1-methylpyrrolidin-2-one.

of **1a**) in DMF (entries 1-6), and $Cu(OAc)_2$ showed the best activity (entry 6). Surprisingly, the intramolecular Ullmann-type O-arylation worked very well in the absence of a copper catalyst at 100 °C, and the target product **2a** was isolated in 96% yield (entry 7). This result showed that the copper salts (entries 1–6) actually inhibited the reactivity of the substrate (**1a**). We screened other bases (entries 8–12) and K_2CO_3, Na_2CO_3, and K_3PO_4 provided excellent yields (entries 8–10). Only a small amount of **2a** (8% yield) was afforded in the absence of a base (entry 13). The effect of the solvent was also investigated (compare entries 9 and 14–19), and DMF, DMSO, and NMP were the better solvents, with DMF being the best (entry 9). The yield decreased when the reaction temperature was lowered (compare entries 9 and 20). We used highly pure K_2CO_3 (99.997% purity) to avoid the involvement of other metals in the reaction,[11] and the reaction provided a 95% yield (entry 21), which was similar to the yield when the analytically pure K_2CO_3 (99%) was used. The results above show that the base and solvent are key factors in the intramolecular O-arylation. In fact, the preparation of the substrate **1a** by the reaction of methyl 2-bromobenzoate with 1-(*p*-tolyl)ethanone at 66 °C in THF in the presence of NaH was performed but no intramolecular O-arylation product (**2a**) was observed.[12]

The intramolecular O-arylation of the substituted 1-(2-bromophenyl)-1,3-diones (Table 2, entries 1–17) was first investigated under our optimized reaction conditions (one equivalent of K_2CO_3, DMF, 100 °C, under air), and the examined substrates reacted to give the products in good to excellent yields. For the R^1 substituent on **1**, the substrates with stronger electron-donating groups (such as -CH_3,

Table 2: Synthesis of chromone derivatives.[a]



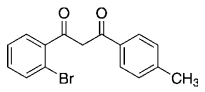
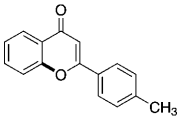
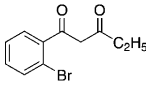
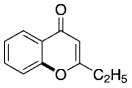
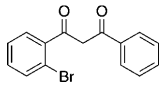
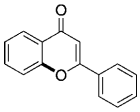
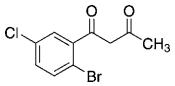
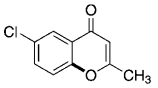
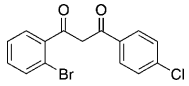
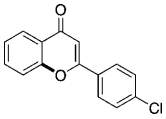
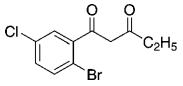
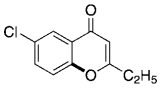
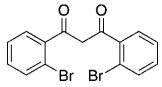
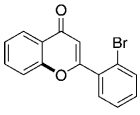
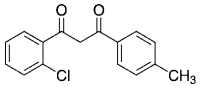
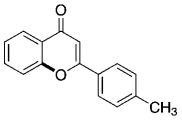
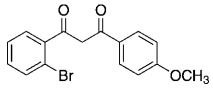
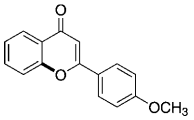
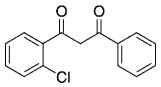
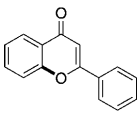
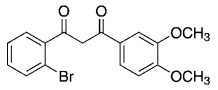
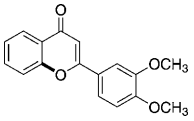
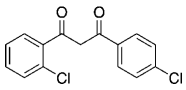
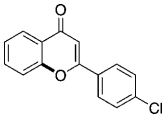
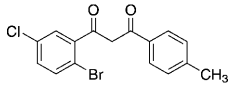
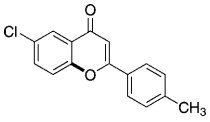
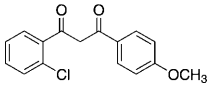
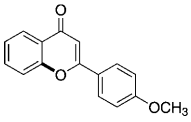
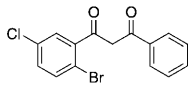
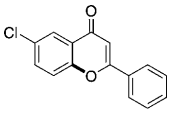
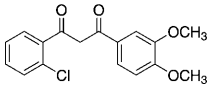
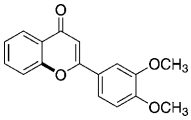
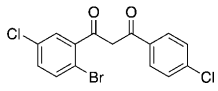
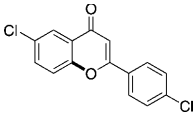
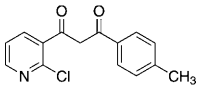
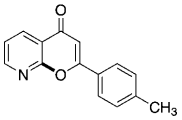
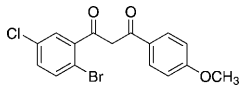
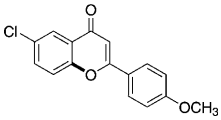
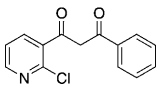
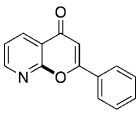
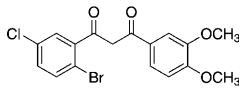
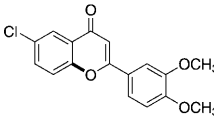
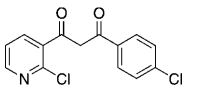
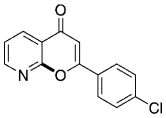
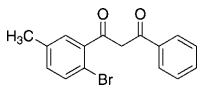
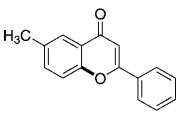
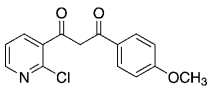
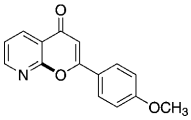
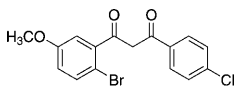
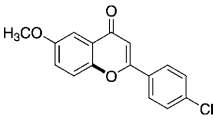
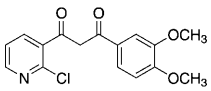
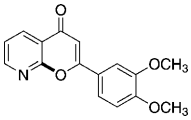
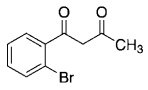
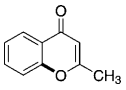
Entry	**1**	**2**[b]		Entry	**1**	**2**[b]	
1		**1a** 	**2a** (97%, 1 h)	15		**1o** 	**2o** (71%, 1 h)
2		**1b** 	**2b** (91%, 1 h)	16		**1p** 	**2p** (72%, 1 h)
3		**1c** 	**2c** (96%, 1 h)	17		**1q** 	**2q** (76%, 1 h)
4		**1d** 	**2d** (92%, 1 h)	18		**1r** 	**2a** (89%, 1.5 h)
5		**1e** 	**2e** (99%, 1 h)	19		**1s** 	**2b** (90%, 1.5 h)

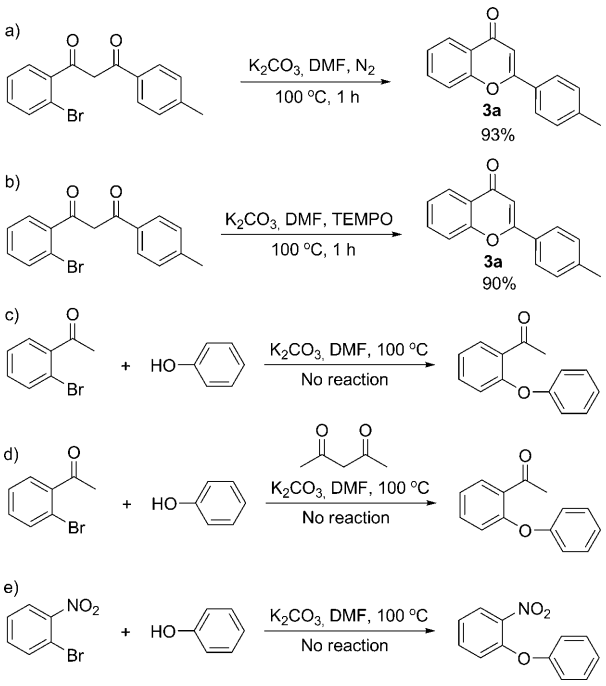
Table 2: (Continued)

Entry	1	2[b]		Entry	1	2[b]	
6		1f		**2f** (96%, 1 h)	20		1t		**2c** (81%, 1.5 h)
7		1g		**2g** (91%, 1 h)	21		1u		**2e** (85%, 1.5 h)
8		1h		**2h** (99%, 1 h)	22		1v		**2f** (93%, 1.5 h)
9		1i		**2i** (79%, 1 h)	23		1w		**2r** (66%, 6 h)
10		1j		**2j** (94%, 1 h)	24		1x		**2s** (70%, 6 h)
11		1k		**2k** (95%, 1 h)	25		1y		**2t** (77%, 6 h)
12		1l		**2l** (85%, 8 h)	26		1z		**2u** (73%, 6 h)
13		1m		**2m** (77%, 12 h)	27		1a′		**2v** (86%, 6 h)
14		1n		**2n** (80%, 1 h)					

[a] Reaction conditions: **1** (0.5 mmol), K_2CO_3 (0.5 mmol), DMF (2 mL), 100 °C, under air. [b] Values in brackets are the yield of isolated product and the reaction time.

-OCH_3) showed lower reactivity (entries 12 and 13). When the R^2 substituent on **1** was an aromatic group (entries 1–13) the products were obtained in higher yields compared to when R^2 was aliphatic (entries 14–17). We extended the scope of substrates to substituted 1-(2-chlorophenyl)-1,3-diones (entries 18–22), and the intramolecular O-arylation occurred in 1.5 hours. This result is particularly interesting because the O-arylation of aryl chlorides was difficult in the previous copper-catalyzed Ullmann-type couplings.[2–5] Inspired by the results above, the intramolecular cyclization of 1-(2-chloropyridin-3-yl)-1,3-dione derivatives was also investigated under the same reaction conditions, and the corresponding target products were obtained in good yields (entries 23–27). The reaction conditions used are very simple, only a common base (K_2CO_3) and solvent (DMF) were required, and the reactions proceeded well under air. The reactions could tolerate some functional groups including halides (entries 3, 4, 7–11, 13, 16, 17, 20, and 25), ethers (entries 5, 6, 10, 11, 13, 21, 22, 26, and 27), and N-heterocycles (entries 23–27).

To explore the reaction mechanism for the synthesis of the chromone derivatives, the following control experiments were performed under the standard reaction conditions (Scheme 2). The intramolecular O-arylation of **1a** performed well under a nitrogen atmosphere (93% yield; Scheme 2a), and this result suggests that the oxygen in air was not involved in the O-arylation reactions of the substrates in Table 2. When the radical scavenger TEMPO was added to the reaction system, the reaction was not affected (Scheme 2b), which implies that the reaction did not proceed via a radical intermediate. We attempted the reaction of 1-(2-bromophenyl)ethanone with phenol in the absence and presence (Scheme 2c and d, respectively) of 2,4-pentanedione (0.2 equiv), and the cross-coupling did not work, which suggests the β-diketone did not mediate the intermolecular O-arylation. When 1-bromo-2-nitrobenzene, which contains a strong electron-withdrawing group, was used as the substrate, the intermolecular O-arylation did not occur (Scheme 2e). This result suggests that it is not only the electron-with-



Scheme 2. Investigation of the reaction mechanism for the synthesis of the chromone derivatives. TEMPO = 2,2,6,6-tetramethylpiperidinyl-1-oxyl.

drawing effect of the carbonyl group (C=O a in **1**; Table 2) ortho to the halide in **1** that influences the occurrence of the intramolecular O-arylation in Table 2, and that the second carbonyl group (C=O c in **1**; Table 2) is also required for the reaction to occur. Further investigations into the reaction mechanism are in progress.

In summary, we have developed a simple, practical, and highly efficient base-promoted method for the synthesis of chromone derivatives. The protocol uses readily available substituted 1-(2-haloaryl)-propane-1,3-diones (synthesized by the reaction of 2-haloarylcarboxylic acid methyl esters with ketones)[12] as the starting materials, inexpensive K_2CO_3 as the base, and DMF as the solvent, and provides the corresponding chromone derivatives in good to excellent yields. The intramolecular Ullmann-type O-arylation method does not need the aid of any transition metal, and therefore avoids contaminating the products with toxic metals. This approach is an inexpensive and environmentally benign way to synthesize chromone derivatives, which are compounds of interest in both academic and industrial research.

Experimental Section

General procedure for synthesis of compounds **2a**–**v**: Substituted 1-(2-haloaryl)-propane-1,3-dione **1** (0.5 mmol), K_2CO_3 (0.5 mmol, 69 mg), and DMF (2 mL) were added to a round bottom flask with a magnetic stirrer. The mixture was stirred under air at 100 °C for 1–12 h (see Table 2). After cooling to room temperature, water was added (10 mL), and then the aqueous solution was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated, and then the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate (10:1 or 7:1)) on silica gel to provide the desired product.

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[11] K_2CO_3 (99.997%) was purchased from Alfa Aesar and contains Mg (2 ppm) and Na (8 ppm); other elements including: Al, Sb, As, Ba, Bi, B, Cd, Ca, Cr, Co, Cu, In, Fe, Pb, Li, Mn, Mo, Ni, P, Si, Te, Sn, Ti, V, Zn, and Zr were not detected (data provided by Alfa Aesar).

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