ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 11256–11258

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Copper-catalyzed *ortho*-acylation of phenols with aryl aldehydes and its application in one-step preparation of xanthones†

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Received 24th August 2012, Accepted 26th September 2012
DOI: 10.1039/c2cc36176k

In the presence of triphenylphosphine, copper(II) chloride can catalyze an intermolecular *ortho*-acylation reaction of phenols with aryl aldehydes. The reaction proceeds smoothly with a wide range of starting materials, and furthermore, it can be used to synthesize xanthone derivatives in a single step in high yields.

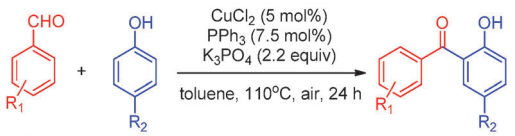
Direct acylation of the aromatic rings of phenols is an important transformation in organic synthesis since phenols are one of the most abundant aromatic compounds in nature and industry.[1] Two major synthetic pathways can be followed in this transformation, namely, the well-known Friedel–Crafts reaction,[2] and the transition-metal-catalyzed C–H activation pathway.[3] However, classical Friedel–Crafts reactions often suffer from harsh reaction conditions and usage of air/water sensitive Lewis acids.[4] While transition-metal-catalyzed C–H activation can convert a carbon–hydrogen bond into carbon–oxygen,[5] carbon–nitrogen,[6] carbon–halide,[7] carbon–sulfur[8] or carbon–carbon bonds,[9] till now, there is only one report about the acylation reaction of unprotected phenols.[10] In that work, Miura and co-workers prepared 2-benzoyl-1-naphthol as a control experiment when they synthesized benzofuran-2(3*H*)-ones; however, no in-depth investigation was reported.

In the process of synthesizing a natural product, SsnB (Sparstolonin B, a xanthone derivative isolated from a Chinese herb showing effective anti-inflammatory activity),[11] an effective *ortho*-acylation of substituted phenol and a facile protocol to form the xanthone ring are needed. Herein, we established a versatile synthetic method in-depth to achieve *ortho*-acylation of phenols firstly, and its application in synthesizing different xanthone derivatives. Xanthones constitute the core of the natural and biologically active family of compounds present in higher plants and microorganisms,[12] as well as the secondary metabolites found in higher plant families and lichens.[13] They exhibit diverse physicochemical and pharmacological properties, such as antitumoral, antibacterial and antiinflammatory.[14]

To investigate the optimized reaction protocol, 3-methoxybenzaldehyde (**1a**) and 4-methoxyphenol (**2a**) were refluxed in toluene for 24 h in the presence of 5 mol% $Pd(OAc)_2$, 7.5 mol% triphenylphosphine and 2.2 equiv. K_2CO_3, and the product (**3aa**) was obtained in 77% yield. With this promising result, a systematic screening of catalysts, ligands, and bases was carried out and the results are summarized in Table S1 (ESI†). Based on the results of Table S1 (ESI†), we chose 1 mmol aldehyde, 1.3 mmol phenol in toluene at 110 °C in the presence of 5 mol% of $CuCl_2$, 7.5 mol% of PPh_3 and K_3PO_4 (2.2 equiv.) as the standard reaction conditions.

We next explored the reaction scope with various phenols and aryl aldehydes, and sixteen *ortho*-acylation products were synthesized (Table 1). The results showed that regardless of the substitution of aryl aldehydes, electron withdrawing or donating, all compounds furnished the desired *ortho*-acylation

Table 1 *ortho*-Acylation of phenols with aryl aldehydes[a]



1a-g 2a-d 3

Entry		R_1		R_2	Product	Yield[b,c] (%)
1	**1a**	3-OCH_3	**2a**	OCH_3	**3aa**	91 (79)
2	**1b**	4-CH_3	**2a**	OCH_3	**3ba**	70 (60)
3	**1c**	H	**2a**	OCH_3	**3ca**	79 (64)
4	**1d**	3-Cl	**2a**	OCH_3	**3da**	83 (70)
5	**1e**	4-F	**2a**	OCH_3	**3ea**	84 (73)
6	**1f**	2,6-OCH_3	**2a**	OCH_3	**3fa**	77 (65)
7	**1a**	3-OCH_3	**2b**	*i*-Pr	**3ab**	94 (82)
8	**1b**	4-CH_3	**2b**	*i*-Pr	**3bb**	73 (60)
9	**1c**	H	**2b**	*i*-Pr	**3cb**	63 (48)
10	**1d**	3-Cl	**2b**	*i*-Pr	**3db**	92 (79)
11	**1g**	4-NO_2	**2b**	*i*-Pr	**3gb**	70 (58)
12	**1a**	3-OCH_3	**2c**	H	**3ac**	56 (47)
13	**1b**	4-CH_3	**2c**	H	**3bc**	64 (50)
14	**1d**	3-Cl	**2c**	H	**3dc**	78 (67)
15	**1g**	4-NO_2	**2c**	H	**3gc**	42 (31)
16[d]	**1g**	4-NO_2	**2d**	I	**3gd**	62 (51)
17	**1a**	3-OCH_3	**2e**	NO_2	—	—

[a] 1 mmol aldehyde and 1.3 mmol phenol. [b] ^{1}H NMR yield. [c] Isolated yield (in parentheses). [d] Cross-coupling reaction between iodine and hydroxyl was observed besides the *ortho*-acylation reaction.

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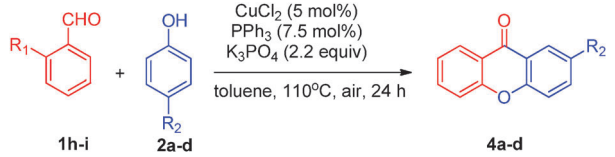
† Electronic supplementary information (ESI) available: Tables S1 and S2, experimental details, data and spectra of MS, ^{1}H NMR, ^{13}C NMR. See DOI: 10.1039/c2cc36176k

Table 2 One-step *ortho*-acylation of phenols with 2-substituted aldehydes to afford xanthones[a]



1h-i 2a-d 4a-d

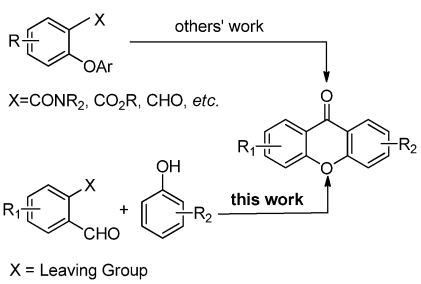
Entry		R_1		R_2	Product	Yield[b,c] (%)
1	**1h**	OCH_3	**2a**	OCH_3	**4a**	85 (71)
2	**1i**	NO_2	**2a**	OCH_3	**4a**	87 (74)
3[d]	**1j**	Br	**2a**	OCH_3	**4a**	68 (52)
4	**1i**	NO_2	**2b**	*i*-Pr	**4b**	92 (81)
5[d]	**1j**	Br	**2b**	*i*-Pr	**4b**	64 (56)
6	**1i**	NO_2	**2c**	H	**4c**	81 (70)
7[d]	**1j**	Br	**2c**	H	**4c**	55 (43)
8	**1i**	NO_2	**2d**	I	**4d**	73 (62)

[a] 1 mmol 2-substituted aldehydes and 1.3 mmol phenol. [b] ^{1}H NMR yield. [c] Isolated yield (in parentheses). [d] Cross-coupling reaction between bromo and hydroxyl groups was observed for entries 3 (17%), 5 (14%) and 7 (13%) besides the *ortho*-acylation reaction.

products in almost similar yields when reacted with the same phenol (70–91%, entries 1–6; 63–94%, entries 7–11; 42–78%, entries 12–15); even for 4-nitrobenzaldehyde, the corresponding product **3gb** was obtained in 70% yield (entry 11). However, the substituted group of phenols played a more important role compared with that of aryl aldehydes. The stronger electron-donating group phenols possessed, the more effective the acylation reactions were. For example, the methoxy and isopropyl substituted phenols (**2a** and **2b**) offered higher yields than unsubstituted phenols (**2c**); conversely with electron-deficient 4-nitrophenol (**2e**), no reaction was detected (entry 17). When 4-iodophenol was used, cross-coupling reaction between iodine and hydroxyl was observed besides the acylation reaction (entry 16).[15] Additionally, aliphatic aldehydes were ineffective to react with phenols (data not shown).

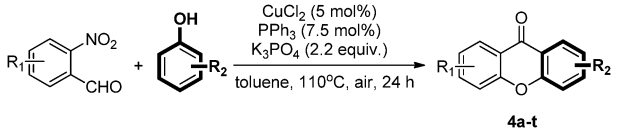
Interestingly, we found that when 2-substituted aryl aldehydes (**1h–j**) reacted with phenols, xanthones were obtained in high yield in one step (Table 2). Albeit many methods are available for the synthesis of xanthones, most of them either require advanced starting materials, exotic reaction conditions, or involve multi-step transformations.[16] There are only a few one-step syntheses of xanthones existing in the literature.[17] Hence our method offers a concise and straightforward strategy to construct xanthones directly without the preactivation of aldehydes (Scheme 1).

As shown in Table 2, 2-methoxybenzaldehyde (**1h**) and 2-nitrobenzaldehyde (**1i**) produced the corresponding xanthones in good yields (62–81%) (entries 1, 2, 4, 6 and 8), while with

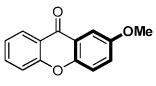
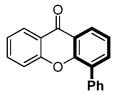
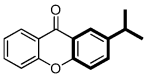
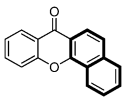
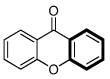
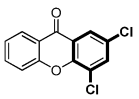
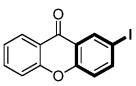
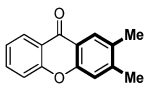
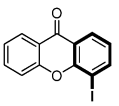
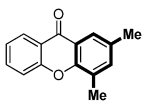
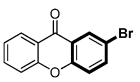
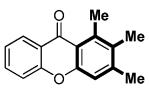
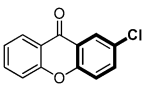
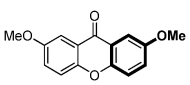
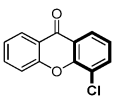
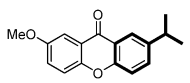
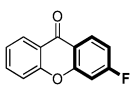
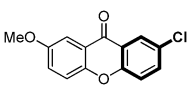
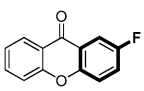
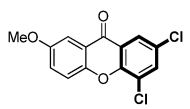


Scheme 1 One-step synthesis of xanthones.

Table 3 Scope of reaction of 2-nitrobenzaldehydes with phenols to prepare xanthones[a]



4a-t

Product		Yield[b,c] (%)	Product		Yield[b,c] (%)
4a		87 (74)	**4k**		69 (55)
4b		92 (81)	**4l**		43 (30)
4c		81 (70)	**4m**		75 (64)
4d		77 (62)	**4n**		84 (72)
4e		73 (62)	**4o**		90 (80)
4f		72 (59)	**4p**		73 (61)
4g		82 (73)	**4q**		83 (70)
4h		76 (60)	**4r**		82 (70)
4i		70 (58)	**4s**		80 (69)
4j		71 (55)	**4t**		68 (57)

[a] 1 mmol 2-nitrobenzaldehydes, 1.3 mmol phenols. [b] ^{1}H NMR yield. [c] Isolated yield (in parentheses).

2-bromobenzaldehyde (**1j**) as the starting material, lower yields were observed, likely due to the cross-coupling reaction between bromo and hydroxyl groups (entries 3, 5 and 7, yields are listed in the footnote). It is believed that the ring-closed xanthone products are achieved *via* the *ortho*-acylation of phenols with 2-substituted aryl aldehydes first, and then under basic conditions, the *ortho*-substituents of aldehydes serving as leaving groups lead to the final ring-closed xanthones.

Since the nitro group gave better results than other leaving groups, the reaction substrates of 2-nitrobenzaldehydes and phenols were investigated (Table 3). It showed that alkoxy, alkyl, aryl and halide substituents were tolerated on the phenols

to furnish the desired xanthones affording moderate to good yields. While an electron-donating group on phenols can promote the reaction, an electron-withdrawing group (NO_2 or CN) will block the reaction completely (data not shown). If the substituted group was at the *para* position of the phenol, the yield was higher than when it was at the *ortho* position, possibly due to the steric effect (**4d** *vs.* **4e**, **4g** *vs.* **4h**). The steric effect can also explain the excellent regioselectivity of this reaction (*e.g.* **4i** was the sole product) as well as the sluggish reactivity of *ortho*-*t*-butylphenol (no product was observed). Disubstituted and trisubstituted xanthones could also be prepared *via* this copper-catalyzed *ortho*-acylation reaction affording moderate yields (**4m–p** and **4t**).

Although the detailed mechanism is not very definitive, it is conceivable that this reaction is a Friedel–Crafts type reaction, which involves the nucleophilic addition of phenols to aldehydes under basic conditions, and then followed by a dehydrogenative oxidation in air to give *ortho*-acylation products.[11,18] If *ortho*-substituents of aldehydes are good leaving groups, ring-closed xanthones will form automatically. During this process, copper (serving as a Lewis acid) may interact with the phenol oxygen and stabilize the intermediates which lead to a smooth transformation.

In summary, we first demonstrated an intermolecular catalytic *ortho*-acylation of phenols with various aryl aldehydes in-depth using copper(II) as the catalyst in the presence of triphenylphosphine. Furthermore, this method can be used to synthesize xanthones in one step in high yield. We are currently investigating the expansion of this *ortho*-acylation strategy to a broader scope of substrates.

This project is partially supported by an NIH grant R21AT006767 (DF).

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