Published in final edited form as:

Chem Commun (Camb). 2012 November 25; 48(91): 11256–11258. doi:10.1039/c2cc36176k.

Copper-Catalyzed *Ortho*-Acylation of Phenols with Aryl Aldehydes and Its Application in One-Step Preparation of Xanthenes

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Abstract

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 with 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 the harsh reaction condition and usage of air/water sensitive Lewis acid.⁴ While transition-metal-catalyzed C-H activation can convert carbon-hydrogen bond into carbon-oxygen,⁵ carbon-nitrogen,⁶ carbon-halide,⁷ carbon-sulfur⁸ 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(3H)-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. Xanthenes constitute the core of 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

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[†]Electronic Supplementary Information (ESI) available: Table S1, Table S2, experimental details, data and spectra of Ms, ¹H NMR, ¹³C NMR. See DOI: 10.1039/b000000x/

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 K₂CO₃, 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 summarized in Table S1. Based on the results of Table S1, we chose 1 mmol aldehyde, 1.3 mmol phenol in toluene at 110 °C in the presence of 5 mol% of CuCl₂, 7.5 mol% PPh₃ and K₃PO₄ (2.2 equiv.) as the standard reaction condition.

We next explored the reaction scope with various phenols and aryl aldehydes, and seventeen *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 products in almost similar yields when reacted with the same phenol (70–91% entries 1–7; 63–94% entries 8–12; 42–78% entries 13–16); even 4-nitrobenzaldehyde, the corresponding product **3gb** was obtained with 70% yield (entry 12). However, the substituted group of phenols played a more important role compared with that of aryl aldehyde. 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 phenol (**2c**); conversely with electro-deficient 4-nitrophenol (**2e**), no reaction was detected (entry 18). When 4-iodophenol was used, cross-coupling reaction between iodine and hydroxyl was observed besides the acylation reaction (entry 17).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, xanthenes were obtained with high-yield in one step (Table 2). Albeit many methods are available for the synthesis of xanthenes, most of them either require advanced starting materials, exotic reaction conditions, or involve multistep transformations.¹⁶ There are only a few one-step synthesis of xanthenes existing in literature.¹⁷ Hence our method offers a concise and straightforward strategy to construct xanthenes directly without the preactivation of aldehydes (Scheme 1).

As shown in Table 2, 2-methoxybenzaldehyde (**1h**) and 2-nitrobenzaldehyde (**1i**) produced the corresponding xanthenes in good yields (62–81%) (entries 1, 2, 4, 6 and 8), while with 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 a basic condition, the *ortho*-substituents of aldehydes serving as leaving groups lead to the final ring-closed xanthenes.

Since 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 xanthenes affording moderate to good yields. While an electron-donating groups on phenols can promote the reaction, an electron-withdrawing groups (NO₂ 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 it was at *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 was as the sluggish reactivity of *ortho*-*t*-butylphenol (no product was observed). Disubstituted and trisubstituted xanthenes 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 condition, 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 xanthenes will form automatically. During this process, copper (serve 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 presence of triphenylphosphine. Furthermore, this method can be used to synthesize xanthenes in one step with high-yield. We are currently investigating the expansion of this *ortho*-acylation strategy to a broader scope of substrates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Notes and references

- (a) Weber, M.; Kleine-Boymann, M. "Phenol" in Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VCH; 2004. (b) Koehler K, Gordon S, Brandt P, Carlsson B, Backsbro-Saeidi A, Apelqvist T, Agback P, Grover GJ, Nelson W, Grynfarb M, Farnegardh M, Rehnmark S, Malm J. J. Med. Chem. 2006; 49:6635. [PubMed: 17154490] (c) Gan FF, Chua YS, Scarmagnani S, Palaniappan P, Franks M, Poobalasingam T, Bradshaw TD, Westwell AD, Hagen T. Biochem. Biophys. Res. Commun. 2009; 387:741. [PubMed: 19635456] (d) Finkelstein BL, Benner EA, Hendrixson MC, Kranis KT, Rauh JJ, Sethuraman MR, McCann SF. Bioorg. Med. Chem. 2002; 10:599. [PubMed: 11814848] (e) Zhang L, Zhang JY. J. Comb. Chem. 2006; 8:361. [PubMed: 16677006] (f) Rao HH, Li CJ. Angew. Chem. Int. Ed. 2011; 50:8936.
- (a) Rappoport, Z. The Chemistry of Phenols. Weinheim: Wiley-VCH; 2003. (b) Tyman, JHP. Synthetic and Natural Phenols. New York: Elsevier; 1996.
- (a) Lewis LN, Smith JF. J. Am. Chem. Soc. 1986; 108:2728. (b) Lyons TW, Sanford MS. Chem. Rev. 2010; 110:1147. [PubMed: 20078038] (c) Ritleng V, Sirlin C, Pfeffer M. Chem. Rev. 2002; 102:1731. [PubMed: 11996548] (d) Davies HML, Du Bois J, Yu JQ. Chem. Soc. Rev. 2011; 40:1855. [PubMed: 21390392] (e) Bedford RB, Cazin CSJ, Holder D. Coord. Chem. Rev. 2004; 248:2283. (f) Sengupta S, Shi X. ChemCatChem. 2010; 2:609. (g) Huang K, Sun CL, Shi ZJ. Chem. Soc. Rev. 2011; 40:2435. [PubMed: 21387036] (h) Racowski JM, Ball ND, Sanford MS. J. Am. Chem. Soc. 2011; 133:18022. [PubMed: 22017502] (i) Zhang G, Luo Y, Wang Y, Zhang L. Angew. Chem. Int. Ed. 2011; 50:4450.
- (a) Guo X, Li W, Li Z. Eur. J. Org. Chem. 2010:5787. (b) Oelgemöller M, Schiel C, Fröhlich R, Mattay J. Eur. J. Org. Chem. 2002:2465.
- (a) Dick AR, Hull KL, Sanford MS. J. Am. Chem. Soc. 2004; 126:2300. [PubMed: 14982422] (b) Desai LV, Stowers KJ, Sanford MS. J. Am. Chem. Soc. 2008; 130:13285. [PubMed: 18781752] (c) Donald WA, McKenzie CJ, O'Hair RAJ. Angew. Chem. Int. Ed. 2011; 50:8379. (d) Uhl W, Vinogradov A, Grimme S. J. Am. Chem. Soc. 2007; 129:11259. [PubMed: 17705491]
- (a) Thu HY, Yu WY, Che CM. J. Am. Chem. Soc. 2006; 128:9048. [PubMed: 16834374] (b) Dick AR, Remy MS, Kampf JW, Sanford MS. Organometallics. 2007; 26:1365. (c) Yan W, Wang Q, Chen Y, Petersen JL, Shi X. Org. Lett. 2010; 12:3308. [PubMed: 20617810] (d) Zhong C, Shi X. Eur. J. Org. Chem. 2010:2999. (e) Lu B, Li C, Zhang L. J. Am. Chem. Soc. 2010; 132:14070. [PubMed: 20853846]
- (a) Oi S, Vatanabe S, Fukita S, Inoue Y. Tetrahedron Lett. 2003; 44:8665. (b) Kalyani D, Dick AR, Anani WQ, Sanford MS. Org. Lett. 2006; 8:2523. [PubMed: 16737304] (c) Wan WB, Ma ZX, Li BJ, Zhang KY, Cao SK, Zhang SW, Shi ZJ. J. Am. Chem. Soc. 2006; 128:7416. [PubMed: 16756276] (d) Chen X, Hao XS, Goodhue CE, Yu JQ. J. Am. Chem. Soc. 2006; 128:6790. [PubMed: 16719450] (e) Mei TS, Giri R, Maugel N, Yu JQ. Angew. Chem. Int. Ed. 2008; 47:5215.

8. (a) Inamoto K, Arai Y, Hiroya K, Doi T. *Chem. Commun.* 2008;5529.(b) Inamoto K, Hasegawa C, Hiroya K, Doi T. *Org. Lett.* 2008; 10:5147. [PubMed: 18947183] (c) Joyce LL, Batey RA. *Org. Lett.* 2009; 11:2792. [PubMed: 19476320] (d) Zhao X, Dimitrijevic E, Dong VM. *J. Am. Chem. Soc.* 2009; 131:3466. [PubMed: 19243177]
9. (a) Kalyani D, Deprez NR, Desai LV, Sanford MS. *J. Am. Chem. Soc.* 2005; 127:7330. [PubMed: 15898779] (b) Deng GJ, Zhao L, Li CJ. *Angew. Chem. Int. Ed.* 2008; 47:6278.(c) Zhao XD, Yu ZK. *J. Am. Chem. Soc.* 2008; 130:8136. [PubMed: 18540607] (d) Tsai AS, Bergman RG, Ellman JA. *J. Am. Chem. Soc.* 2008; 130:6316. [PubMed: 18444613] (e) Giri R, Yu JQ. *J. Am. Chem. Soc.* 2008; 130:14082. [PubMed: 18834125] (f) Campeau LC, Schipper DJ, Fagnou K. *J. Am. Chem. Soc.* 2008; 130:3266. [PubMed: 18293986] (g) Wu Y, Li B, Mao F, Li X, Kwong FY. *Org. Lett.* 2011; 13:3258. [PubMed: 21598959]
10. Satoh T, Tsuda T, Terao Y, Miura M, Nomura M. *J. Mol. Catal. A: Chem.* 1999; 143:203.
11. Liang Q, Wu Q, Jiang J, Duan J, Wang C, Smith MD, Lu H, Wang Q, Nagarkatti P, Fan D. *J. Bio. Chem.* 2011; 286:26470. [PubMed: 21665946]
12. (a) Takahashi N, Kanayama T, Okuyama K, Kataoka H, Fukaya H, Suzuki K, Matsumoto T. *Chem. Asian. J.* 2011; 6:1752. [PubMed: 21557490] (b) Suzuki Y, Fukuta Y, Ota S, Kamiya M, Sato M. *J. Org. Chem.* 2011; 76:3960. [PubMed: 21469707] (c) Kondo M, Zhang LL, Ji HP, Kou Y, Ou BX. *J. Agric. Food Chem.* 2009; 57:8788. [PubMed: 19807152] (d) Barbero N, SanMarin R, Dominguez E. *Green Chem.* 2009; 11:830.(e) Barber N, SanMarin R, Dominguez E. *Tetrahedron.* 2009; 65:5729.
13. Cardona ML, Fernandez MI, Pedro JR, Serrano A. *Phytochemistry.* 1990; 29:3003.
14. (a) Woo S, Jung J, Lee C, Kwon Y, Na Y. *Bioorg. Med. Chem. Lett.* 2007; 17:1163. [PubMed: 17194586] (b) Matsumoto K, Akao Y, Ohguchi K, Ito T, Tanaka T, Iinuma M, Nozawa Y. *Bioorg. Med. Chem.* 2005; 13:6064. [PubMed: 16112579] (c) Schwaebke MK, Moran TJ, Whitten JP. *Tetrahedron Lett.* 2005; 46:827.(d) Pedro M, Cerqueira F, Sousa ME, Nascimento MSJ, Pinto M. *Bioorg. Med. Chem.* 2002; 10:3725. [PubMed: 12413829] (e) Cardona ML, Fernandez MI, Pedro JR, Serrano A. *Phytochemistry.* 1990; 29:3003.(f) Peres V, Nagem TJ, Faustino de Oliveira F. *Phytochemistry.* 2000; 55:683. [PubMed: 11190384] (g) Kenji M, Yukihiro A, Hong Y, Kenji O, Tetsuro I, Toshiyuki T, Emi K, Munekazu I, Yoshinori N. *Bioorg. Med. Chem.* 2004; 12:5799. [PubMed: 15498656]
15. (a) Burgos CH, Barder TE, Huang X, Buchwald SL. *Angew. Chem. Int. Ed.* 2006; 45:4321.(b) Bedford RB, Limmert ME. *J. Org. Chem.* 2003; 68:8669. [PubMed: 14575501]
16. (a) Grover PK, Shah GD, Shah RC. *J. Chem. Soc.* 1955:3982.(b) Jackson WT, Robert JB, Froelich LL, Gapinski DM, Mallett BE, Sawyer JS. *J. Med. Chem.* 1993; 36:1726. [PubMed: 8389876] (c) Familoni OB, Ionica I, Bower FJ, Snieckus V. *Synlett.* 1997:1081.(d) Hassall CH, Lewis JR. *J. Chem. Soc.* 1961:2312.
17. (a) Wang S, Xie K, Tan Z, An X, Zhou X, Guo C, Peng Z. *Chem. Commun.* 2009:6469.(b) Okuma K, Nojima A, Matsunaga N, Shioji K. *Org. Lett.* 2009; 11:169. [PubMed: 19053733] (c) Zhao J, Larock RC. *Org. Lett.* 2005; 7:4273. [PubMed: 16146405] (d) Zhao J, Larock RC. *J. Org. Chem.* 2007; 72:583. [PubMed: 17221977] (e) Zhang H, Shi R, Gan P, Liu C, Ding A, Wang Q, Lei A. *Angew. Chem. Int. Ed.* 2012; 51:5204.(f) Zhao J, Yue D, Campo MA, Larock RC. *J. Am. Chem. Soc.* 2007; 129:5288. [PubMed: 17397167] (g) Wang P, Rao H, Hua R, Li CJ. *Org. Lett.* 2012; 14:902. [PubMed: 22272652]
18. (a) Satoh T, Tsuda T, Kushino Y, Miura M, Nomura M. *J. Org. Chem.* 1996; 61:6476. [PubMed: 11667500] (b) Tamaru Y, Yamada Y, Inoue K, Yamamoto Y, Yoshida Z. *J. Org. Chem.* 1983; 48:1286.(c) Nagata W, Okada K, Aoki T. *Synthesis.* 1979:365.

Scheme 1.
One-step synthesis of xanthenes

Table 1

Ortho-acylation of phenols with aryl aldehydes ^a

entry	R ₁	R ₂	product	Yield (%) ^{b, c}	
1	1a	3-OCH ₃	3aa	91 (79)	
2	1b	4-CH ₃	3ba	70 (60)	
3	1c	H	3ca	79 (64)	
4	1d	3-Cl	3da	83 (70)	
5	1e	4-F	3ea	84 (73)	
7	1f	2,6-OCH ₃	3fa	77 (65)	
8	1a	3-OCH ₃	3ab	94 (82)	
9	1b	4-CH ₃	3bb	73 (60)	
10	1c	H	3cb	63 (48)	
11	1d	3-Cl	3db	92 (79)	
12	1g	4-NO ₂	3gb	70 (58)	
13	1a	3-OCH ₃	3ac	56 (47)	
14	1b	4-CH ₃	3bc	64 (50)	
15	1d	3-Cl	3dc	78 (67)	
16	1g	4-NO ₂	3gc	42 (31)	
17 ^d	1g	4-NO ₂	3gd	62 (51)	
18	1a	3-OCH ₃	2e	NO ₂	-

^a 1 mmol aldehyde and 1.3 mmol phenol;^b ¹H NMR yield;^c Isolated yield (in parenthesis);

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^d Cross-coupling reaction between iodine and hydroxyl was observed besides the *ortho*-acylation reaction.

Table 2
One-step *ortho*-acylation of phenols with 2-substituted aldehydes to afford xanthenes ^a

entry	R ₁	R ₂	product	Yield % ^{b, c}
1	1h	OCH ₃	4a	85 (71)
2	1i	NO ₂	4a	87 (74)
3 ^d	1j	Br	4a	68 (52)
4	1i	NO ₂	4b	92 (81)
5 ^d	1j	Br	4b	64 (56)
6	1i	NO ₂	4c	81 (70)
7 ^d	1j	Br	4c	55 (43)
8	1i	NO ₂	4d	73 (62)

^a 1 mmol 2-substituted aldehydes and 1.3 mmol phenol;

^b ¹H NMR yield;

^c Isolated yield (in parenthesis);

^d Cross-coupling reaction between bromo and hydroxyl was observed in entries 3 (17%), 5 (14%) and 7 (13%) besides the *ortho*-acylation reaction.

Table 3

Scope of reaction of 2-nitrobenzaldehydes with phenols to prepare xanthenes ^a

Product	Yield (%) ^{b, c}	Product	Yield (%) ^{b, c}
87 (74)		69 (55)
92 (81)		43 (30)
81 (70)		75 (64)
77 (62)		84 (72)
73 (62)		90 (80)
72 (59)		73 (61)
82 (73)		83 (70)
76 (60)		82 (70)
70 (58)		80 (69)

Product	Yield (%) ^{b, c}	Product	Yield (%) ^{b, c}
4j	71 (55)	4t	68 (57)

^a 1 mmol 2-nitrobenzaldehydes, 1.3 mmol phenols;

^b ¹H NMR yield;

^c Isolated yield (in parenthesis).