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ARTICLE TYPE

Directing Group Assisted Copper-Mediated Aroylation of Phenols Using 2-Bromoacetophenones

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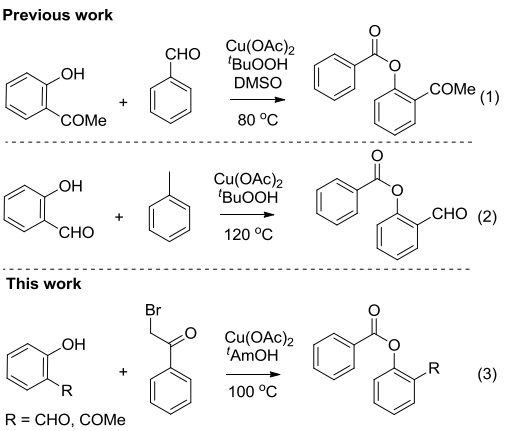
A new directing group assisted method for the synthesis of aryl esters is described. In this Cu(II)-mediated reaction, 2-formylphenols and 2-acetylphenols are easily converted to the aryl esters by treatment with a new aroylating agent 2-bromoacetophenone. In addition, a new external bromine free method for the synthesis of important synthons 2,2-dibromoacetophenones from 2-bromoacetophenones is described.

Aryl esters are common building blocks in organic synthesis and are key motifs in a wide range of natural products, pharmaceuticals and agrochemicals. These esters are typically synthesized by the reaction of acyl halides, anhydrides or activated esters with phenols.[1] Recently, some of the transition-metal-catalyzed reactions such as Pd-catalyzed carbonylative coupling reaction of aryl halides with phenols and Cu-mediated Chan-Lam reactions of carboxylic acids have been developed for the aryl ester synthesis.[2] Beside these reactions, transition-metal-catalyzed cross dehydrogenative coupling reactions (CDC) have also been employed for the synthesis of aryl esters.[3] The directing group assisted synthesis of aryl esters and carbamate esters are known in the literature.[4] However, there are only two such directing group assisted synthesis of aryl esters reported in the literature, using phenols containing acetyl or aldehyde functionality as the directing group and arylaldehyde or alkylbenzene as the coupling partner (eqns 1 & 2, Scheme 1).[4,5] 2-Bromoacetophenones, which have been used effectively for the alkylation of phenols, have never been used for esterification of phenols.[6] In continuation of our work on metal-catalyzed functionalization reactions,[7] we report herein an unprecedented Cu(II)-mediated coupling reaction of *ortho*-formyl/acetyl substituted phenols with 2-bromoacetophenones for the synthesis of aryl esters. Mechanistic investigations revealed that 2,2-dibromoacetophenones generated from 2-bromoacetophenones are key intermediates of this reaction. These 2,2-dibromoacetophenones are very important compounds owing to their frequent use as stating materials in organic synthesis for the construction of important heterocycles, small rings and compounds with a double or triple bond.[8] All synthetic methods to access 2,2-dibromoacetophenones are based on the use of molecular bromine or bromo derivatives or HBr as an external bromine source. However, these methods are not considered to be friendly owing to their unfavorable properties such as toxicity, corrosivity, difficulty in handling, mixture of products formation and high cost of the bromo derivatives.[9] This present study on the esterification reaction also helped us develop an external bromine-free new route for these 2,2-dibromoacetophenones, which is also reported herewith.



Scheme 1. Directing group assisted aroylation of phenols

In preliminary experiments, equimolar amounts of copper salts were utilized to perform the coupling reaction of salicylaldehyde **1a** and 2-bromoacetophenone **2a** (Table 1). Among the copper salts that were tested (entries 1-4), $Cu(OAc)_2$ provided the highest yield of arylester **3aa**[5] (entry 3). Screening of some other protic and aprotic solvents could not improve the yield of **3aa** (entries 5-7). Similarly, further screening of some commonly used oxidants and molecular sieves as additive could not further improve the yield of **3aa** (entries 8-12), though the oxidants $K_2S_2O_8$ and O_2 provided good yields of **3aa** (entries 8,11).

With the optimized reaction conditions in hand, we first tested the scope of this coupling reaction of **2a** with various salicylaldehydes **1a-i** (Table 2). All the tested salicylaldehydes substituted with electron-donating and electron-withdrawing groups such as methyl, *tert*-butyl, methoxy, ethoxy and fluoro were well tolerated irrespective of their position on the aromatic ring providing esters **3aa**-**fa**,**3ha**. Similarly, sensitive functional groups such as allyl and hydroxyl groups were also well tolerated

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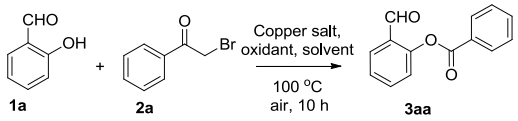
Table 1. Optimization of the reaction conditions[a]



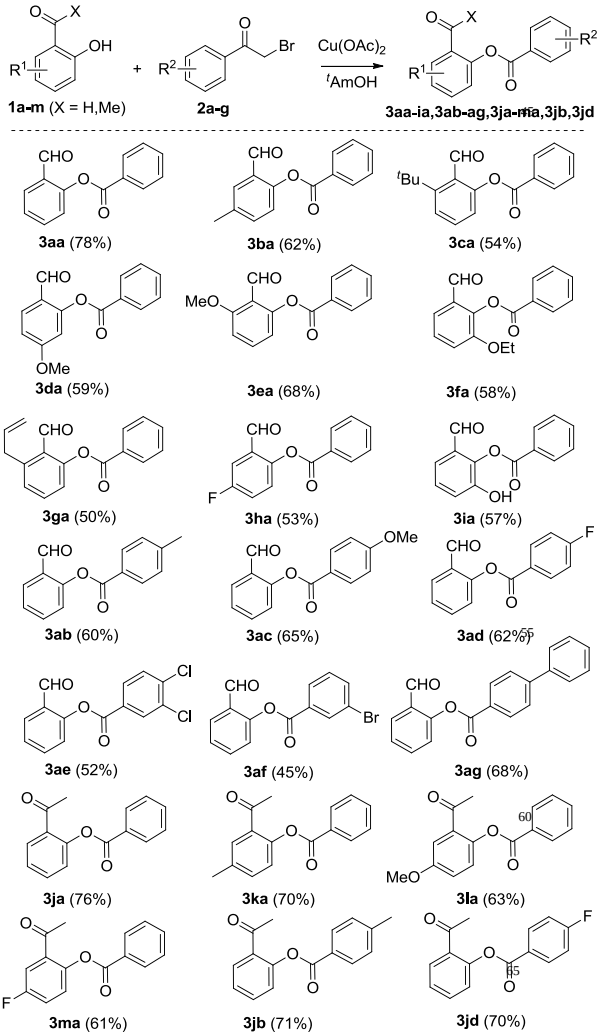
entry	[Cu]	oxidant	solvent	**3aa** (%)[b]
1	$CuCl_2$	-	^{t}AmOH	21
2	$Cu(OTf)_2$	-	^{t}AmOH	60
3	$Cu(OAc)_2$	-	^{t}AmOH	78
4	CuI	-	^{t}AmOH	23
5	$Cu(OAc)_2$	-	H_2O	19
6	$Cu(OAc)_2$	-	^{i}PrOH	54
7	$Cu(OAc)_2$	-	Toluene	16
8[c]	$Cu(OAc)_2$	$K_2S_2O_8$	^{t}AmOH	70
9[c]	$Cu(OAc)_2$	Ag_2O	^{t}AmOH	34
10[c,d]	$Cu(OAc)_2$	TBHP	^{t}AmOH	56
11[c]	$Cu(OAc)_2$	O_2	^{t}AmOH	64
12[e]	$Cu(OAc)_2$	-	^{t}AmOH	74

[a]*Reaction conditions*: **1a** (1.0 mmol), **2a** (2.0 mmol), copper salt (1.0 mmol), oxidant (1.0 mmol) and solvent (6 mL) at 100 °C under air for 10 h; unless otherwise mentioned. [b]Yield of isolated product. [c]30 mol% catalyst. [d]TBHP in decane. [e]Molecular sieves (3.0 equiv) were used.

to provide esters **3ga**,**3ia**. The selective protection of 2-hydroxyl group in the presence of 3-hydroxyl group shows the directive group effect in this coupling reaction. The selective protection of hydroxy functionality of salicylaldehyde as aryl ester in the presence of other hydroxyl groups in the salicylaldehyde molecule is a important transformation in bioactive natural product synthesis.[10] Next, some of the 2-bromoacetophenones having electron-donating and electron-withdrawing groups such as methyl, methoxy, fluoro, chloro, bromo and phenyl on the aromatic ring (**2b-g**) were also tested to provide the corresponding esters **3ab-ag** in moderate yields. Then, the scope of this coupling reaction was studied with phenols that contain an acetyl group as the directing group. These 2-hydroxy acetophenones **1j-m** turned out to be good substrates for this coupling reaction. Thus, 2-hydroxy acetophenones with substituents such as methyl, methoxy and fluoro or without substituent on the aryl ring (**1j-m**) provided good yields of the ketoesters **3ja-ma**[5]. Similarly, representative 2-bromoacetophenones substituted with methyl and fluoro groups on the aromatic ring **2b**,**2d** were also found to be good substrates to provide ketoesters **3jb-jd**.

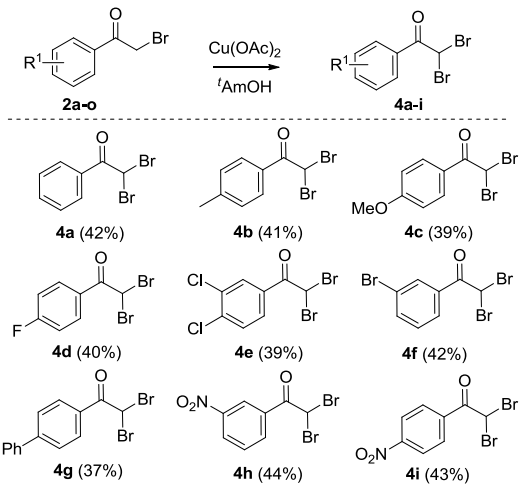
To study the mechanism of the reaction, the standard reaction conditions were applied to **2a** alone in the absence of the phenolic partner **1**. This reaction provided 2,2-dibromoacetophenone **4a**[8a] in 42% yield in five hours, indicating **4a** to be the key intermediate of this reaction. As 2,2-dibromoacetophenones are very important substrates in organic synthesis, we applied this external bromine-free reaction conditions for the synthesis of a series of 2,2-dibromoacetophenones. As shown in Table 3, 2-bromoacetophenones possessing substituents such as methyl, methoxy, fluoro, chloro, phenyl and sensitive substituents such as

Table 2. Substrate scope studies



[a]*Reaction conditions:* **1** (1.0 mmol), **2** (2.0 mmol) and $Cu(OAc)_2$ (1.0 equiv) in ^{t}AmOH (6.0 mL) was heated at 100 °C for 10 h under air.

Table 3. Synthesis of 2,2-dibromoacetophenones



[a]*Reaction conditions:* **2** (2.0 mmol) and $Cu(OAc)_2$ (1.0 mmol) in ^{t}AmOH (6.0 mL) was heated at 100 °C for 5 h under air.

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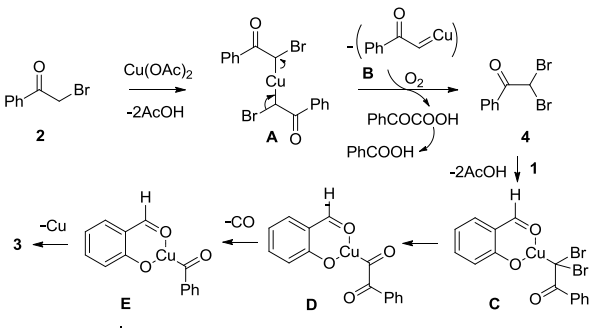

Scheme 2. Possible reaction mechanism

bromo and nitro were found to be very good substrates to provide dibromoacetophenone **4a-i**. In the reaction mixture of **1a** and **2a**, the presence of 2,2-dibromoacetophenone, phenylglyoxalic acid and benzoic acid was determined by thin layer chromatography after four hours. In the absence of the directing group, reaction of simple phenol with **2a** could not provide the corresponding aryl ester. Furthermore, the reaction of **1a** and **2a** under the standard conditions and in the presence of argon provided 43% yield of **3aa**, indicating the requirement of oxygen for the reaction to progress. Again, the same reaction when performed under oxygen balloon, surprisingly, could not provide the desired compound **3aa**, instead benzoic acid was isolated as the main product. In a separate experiment of compound **4a** under air, with one equivalent of $Cu(OAc)_2$ in ^{t}AmOH, provided a mixture of phenylglyoxalic acid and benzoic acid (14%) in six hours at 100 ^{o}C. Probably, the Cu(II)-mediated conversion of 2-bromoacetophenone to phenyl glyoxalic acid and finally to benzoic acid via 2,2-dibromoacetophenone is faster in the presence of excess oxygen. Again, the reaction of **1a** and 2,2-dibromoacetophenone (**4a**) under the optimized reaction conditions afforded the same aryl ester **3aa** in 70% yield. Under the same conditions, reaction of **1a** with phenylglyoxalic acid afforded only 11% of **3aa** and reaction of **1a** with benzoic acid did not work. Based on these observations and literature precedents,[11] a possible mechanism is proposed for this reaction which is shown in Scheme 2. In the presence of Cu(II), initially, two molecules of **2** form Cu(II)-complex **A**, which on subsequent cleavage affords complex **B** and compound **4**. In the presence of air, complex **B** forms phenylglyoxalic acid and benzoic acid.[11a-c] The carbonyl directed activation of phenolic hydroxyl group in the presence of Cu(II) and removal of the acidic proton of **4** affords complex **C**. Further hydrolysis of dibromo compound **C** in the presence of Cu and oxygen provides dicarbonyl Cu(II)-complex D,[11f] which on decarbonylation and reductive elimination of Cu affords the final compound **3**.

In summary, we have developed a new method for the directing group assisted synthesis of aryl esters. In this copper(II)-mediated reaction, *ortho*-formyl and *ortho*-acetyl substituted phenols were converted to aryl esters by using 2-bromoacetophenones as novel but readily available aroylating agent. In addition, we developed a new copper(II)-mediated bromine free reaction conditions for the synthesis of very important motif 2,2-dibromoacetophenones from 2-bromoacetophenones, which should be of synthetic utility.

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.†Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of synthesized compounds. See DOI:

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A new method for directing group-assisted synthesis of aryl esters and an external bromine free synthesis of 2,2-dibromoacetophenones is described.