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# Copper-catalyzed three-component reactions of phenols, acyl chlorides and Wittig reagents for the synthesis of β-aryloxyl acrylates†

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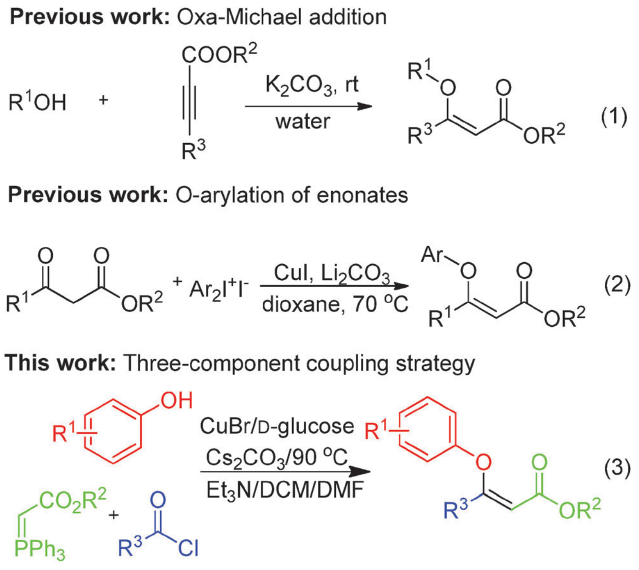
**The synthesis of aryloxyl acrylates has been achieved through a new three-component synthetic method involving the assembly of phenols, acyl chlorides and Wittig reagents in the presence of a copper catalyst using glucose as a green ligand. β-Aryloxyl acrylates have been prepared with high diversity and in good to excellent yields involving the cascade formation of a new C═C bond and a C(sp$^2$)–O bond.**

β-Aryloxyl acrylates and analogous compounds constitute a class of important organic compounds. They have been broadly involved as either main building blocks or key intermediates in the synthesis of numerous useful organic products.[1] In addition, the polar C═C bond in these acrylates is a potential highly reactive site that can be used for the rational design of new synthetic reactions. According to the known literature, β-aryloxyl acrylates have been prepared by employing several different synthetic approaches such as the oxa-Michael addition of phenols to propiolates (eqn (1), Scheme 1),[2] the copper-catalyzed *O*-arylation of enonates (eqn (2), Scheme 1),[3] and the coupling of phenols with haloacrylates.[4] While these methods constitute the main current options towards the synthesis of β-aryloxyl acrylates, these two-component protocols suffer from the common limitation of low product diversity since only the two reaction partners allow structural variation. In this regard, devising a diversity oriented synthetic tactic is of significant urgency in the field of β-aryloxyl acrylate chemistry.

Multicomponent reactions (MCRs) employ three or more reactants to assemble the desired products in one vessel with one set of reaction conditions fixed in one operation. The unique advantages of MCRs lie in their power to furnish multiple chemical transformations (bond cleavage and formation) in one-pot, and the rapid generation of chemical products with significant structural diversity and complexity.[5] Owing to their exceptional step economy and low chemical/energy consumption, MCRs have now been well recognized as an important sustainable synthetic strategy.[6] Therefore, following our long-standing interest in the chemistry of MCRs,[7] and in order to develop diversity oriented synthetic methodologies toward the synthesis of β-aryloxyl acrylates, we report herein a three-component protocol for the synthesis of structurally diverse products using simple starting materials consisting of phenols, Wittig reagents and acyl chlorides *via* the functionalization of the sp$^2$C (CO)–Cl bond.[8] The construction of the desired product consists of a Wittig reaction/phenol vinylation cascade using CuBr as catalyst and glucose as a naturally green ligand[9] (eqn (3), Scheme 1).



Scheme 1 Different routes to aryloxyl acrylates.

At the beginning, the investigation started from running the model reaction of phenol **1a**, Wittig reagent **2a** and acetyl chloride **3a**. It was found that the presence of a copper catalyst, CuBr, a ligand 1,10-phenanthroline (**L1**) and Et$_3$N/Cs$_2$CO$_3$ as the base

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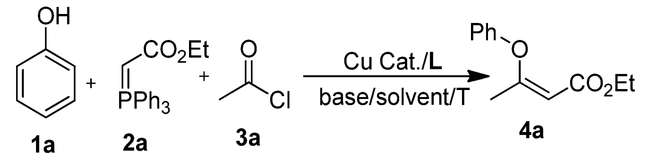
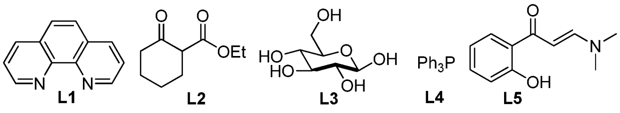
† Electronic supplementary information (ESI) available: General information, experimental procedure, characterization data, $^1$H and $^{13}$C NMR spectra for all products. See DOI: 10.1039/c4nj02010c

Table 1 Results on optimizing reaction conditions[a]



| Entry | Cat. (mol%) | Ligand | Base | Solvent | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | CuBr | No | $Cs_2CO_3$ | DMSO | 22 |
| 2 | CuBr | **L1** | $Cs_2CO_3$ | DMSO | 30 |
| 3 | CuBr | **L2** | $Cs_2CO_3$ | DMSO | 47 |
| 4 | CuBr | **L3** | $Cs_2CO_3$ | DMSO | 52 |
| 5 | CuBr | **L4** | $Cs_2CO_3$ | DMSO | 35 |
| 6 | CuBr | **L5** | $Cs_2CO_3$ | DMSO | 30 |
| 7 | No | **L3** | $Cs_2CO_3$ | DMSO | 21 |
| 8 | CuI | **L3** | $Cs_2CO_3$ | DMSO | 40 |
| 9 | CuO | **L3** | $Cs_2CO_3$ | DMSO | 37 |
| 10 | $Cu(OAc)_2$ | **L3** | $Cs_2CO_3$ | DMSO | 31 |
| 11[c] | CuBr | **L3** | $Cs_2CO_3$ | DMSO | Trace |
| 12 | CuBr | **L3** | No | DMSO | Trace |
| 13 | CuBr | **L3** | $K_2CO_3$ | DMSO | 40 |
| 14 | CuBr | **L3** | NaOH | DMSO | 36 |
| 15 | CuBr | **L3** | *t*-BuONa | DMSO | 34 |
| 16 | CuBr | **L3** | $Cs_2CO_3$ | DMF | 65 |
| 17 | CuBr | **L3** | $Cs_2CO_3$ | Toluene | 30 |
| 18 | CuBr | **L3** | $Cs_2CO_3$ | Dioxane | 35 |
| 19[d] | CuBr | **L3** | $Cs_2CO_3$ | DMF | 58 |
| 20[e] | CuBr | **L3** | $Cs_2CO_3$ | DMF | 55 |

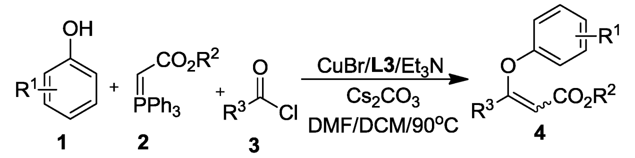


[a] General conditions: **1a** (0.30 mmol), **2a** (0.45 mmol), **3a** (0.45 mmol), $Et_3N$ (0.45 mmol), Cu catalyst (0.03 mmol), ligand (0.06 mmol) and base (0.6 mmol) in an additional solvent (2 mL) together with $CH_2Cl_2$ (2 mL), stirred at 90 °C for 8 h. [b] Yield of isolated products based on **1a**. [c] In the absence of $Et_3N$. [d] Reaction at 100 °C. [e] Reaction at 80 °C.

additive could promote the reaction to produce the desired product **4a**, albeit in a low yield (entries 1 and 2, Table 1). The result inspired us to conduct a systematic optimization of the reaction conditions. Initially, a class of different ligands, including the cyclic ketoester **L2**, D-glucose **L3**, triphenyl phosphine **L4** and the enaminone-based ligand **L5** were employed. Among these ligands, D-glucose **L3** exhibited the best effect in assisting the reaction (entries 3–6, Table 1). Subsequently, different cuprous and cupric catalysts as well as an entry without using a copper catalyst were examined, and no better copper catalyst was identified for the model reaction (entries 7–10, Table 1). A control experiment in the absence of either $Et_3N$ or $Cs_2CO_3$ did not give the desired product in an isolable amount probably because $Et_3N$ was required for the *in situ* generation of the allene intermediate while $Cs_2CO_3$ was the base required to assist copper catalysis.[1b,c] During further examination using different bases (entries 13–15, Table 1) and solvents (entries 16–18, Table 1), $Cs_2CO_3$ and DMF turned out to be the most favorable base and reaction medium, respectively. Finally, variation of the reaction temperature proved that 90 °C was the appropriate temperature (entries 19 and 20, Table 1).

Following the definition of the optimal conditions, an array of different substrates for each component containing various substructures have been employed for the synthesis of the desired products **4**. The results from this section were shown in Table 2.

Table 2 Synthesis of different β-aryloxyl acrylates **4**[a]

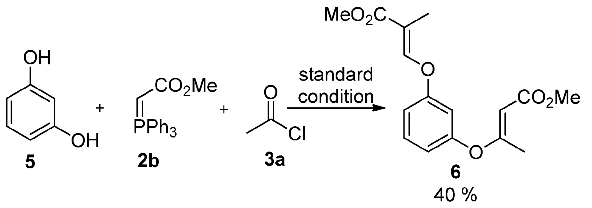


| $R^1$ | $R^2$ | $R^3$ | Product | Yield[b] (%) |
|---|---|---|---|---|
| H | Et | Me | **4a** | 65 |
| 4-Me | Et | Me | **4b** | 49 |
| 4-Cl | Et | Me | **4c** | 58 |
| 4-$CO_2Me$ | Et | Me | **4d** | 48 |
| 2-Cl | Et | Me | **4e** | 60 |
| 2-I | Et | Me | **4f** | 56 |
| 4-Cl | Et | Et | **4g** | 40 |
| 4-Cl | Et | *n*-Pr | **4h** | 45 |
| 4-Br | Et | *n*-Pr | **4i** | 43 |
| H | Me | Me | **4j** | 63 |
| 4-Me | Me | Me | **4k** | 55 |
| 4-$CO_2Me$ | Me | Me | **4l** | 46 |
| 3-COMe | Me | Me | **4m** | 43 |
| H | Me | i-Bu | **4n** | 41 |
| 4-Cl | Me | i-Bu | **4o** | 44 |
| 4-Br | Me | i-Bu | **4p** | 45 |
| 4-Cl | *t*-Bu | Me | **4q** | 47 |

[a] General conditions: **1** (0.30 mmol), **2** (0.45 mmol), **3** (0.45 mmol), $Et_3N$ (0.45 mmol), CuBr (0.03 mmol), **L3** (0.06 mmol) and $Cs_2CO_3$ (0.6 mmol) in $CH_2Cl_2$ (2 mL), DMF (2 mL), stirred at 90 °C for 8 h. [b] Yield of isolated product based on **1**.

It can be seen from the results that the protocol was generally tolerable to the synthesis of β-aryloxyl acrylates **4** employing a variety of different starting materials. Because of the ease of availability, the phenol component displayed the best diversity in providing the desired products, and substituents with either electron-withdrawing and electron-donating properties in different sites were tolerated to give acrylate products in moderate to good yield. Most notably, based on the multicomponent fashion, the easy variation of the acyl chloride component allowed the generation of expanded higher diversity in the ester β-site of the products than most methods previously reported on the synthesis of analogous products. What's more, the products were all obtained with excellent stereoselectivity, as the product was obtained with either the *E* or *Z*-configuration only in every entry.[10]

As an additional example, the entry using resorcinol **5** as the phenol substrate was also examined in the presence of reaction partners **2b** and **3a**. The result from the entry showed that the bisacrylate **6** was the only isolable product under the standard reaction conditions (eqn (4)). However, attempts at employing pyrocatechol and hydroquinone failed to provide the expected products probably because of their tendency to be present as hydroquinone isomers.



(4)

In conclusion, we have developed a copper-catalyzed three-component reaction of phenols, Wittig reagents and acyl chlorides as a new methodology towards the synthesis of β-aryloxyl acrylates. When compared with known synthetic processes, the advantages of the present method lie in the simplicity and ease of availability of all three substrates involved in the process. More notably, the product diversity produced by varying the acyl chloride component allowed the synthesis of a class of new β-aryloxyl acrylates. Therefore, the present method can be a useful option for the synthesis of β-aryloxyl acrylate products.

## Experimental

### General procedure for the synthesis of β-aryloxyl acrylates 4 and 6

In a 25 mL round bottom flask, ylide **2** (0.45 mmol) was dissolved in $CH_2Cl_2$ (2 mL). Acyl chloride **3** (0.45 mmol), $Et_3N$ (0.45 mmol), phenol **1** (0.3 mmol), CuBr (0.03 mmol), **L3** (0.06 mmol), $Cs_2CO_3$ (0.6 mmol) and DMF (2 mL) were then added to the vessel. For the synthesis of **6**, all reagents except phenol and DMF were doubled. The resulting mixture was stirred at 90 °C for 8 h (TLC). The reaction was allowed to stand, cool down to room temperature and 10 mL of water added. The heterogeneous mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried overnight with anhydrous $Na_2SO_4$. The solution was then collected by filtration and the solvent removed under reduced pressure. The residue was subjected to silica gel column chromatography to give the pure desired product using mixed petroleum ether and ethyl acetate ($V_{PET}:V_{EA} = 60:1$).

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