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# Efficient copper-catalyzed Michael addition of acrylic derivatives with primary alcohols in the presence of base†

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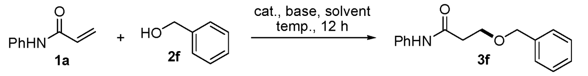
**A novel and efficient copper-catalyzed Michael addition of acrylic derivatives with primary alcohols in the presence of base has been developed. The protocol uses readily available acrylic derivatives and primary alcohols as the starting materials, inexpensive $CuCl_2$ as the catalyst, and the corresponding addition products were obtained in moderate to excellent yields.**

Compounds containing carbon–oxygen bonds widely occur in chemicals and biologically active molecules. Classical construction of carbon–oxygen bonds is from nucleophilic substitution of highly nucleophilic alkoxides to halogenate compounds. Recently, Michael addition of α,β-unsaturated carbonyl compounds with alcohols has attracted much attention,[1] and some efficient methods have been developed, such as organocatalytic,[2] Lewis or Brønsted base (or acid) catalyzed,[3] *N*-heterocyclic carbine-catalyzed,[4] DNA-based catalyzed,[5] transition metal catalyzed,[6] and tetra-*n*-butylammonium fluoride (TBAF) promoted[7] protocols. In the past few decades, copper-catalysts have become popular because of their low-cost and low-toxicity, and great achievement has been made through copper-catalyzed coupling reactions by other groups[8,9] and us.[10] Herein, we report a novel and efficient copper-catalyzed Michael addition of acrylic derivatives with primary alcohols in the presence of base.

Copper-catalyzed Michael addition of *N*-phenylacrylamide (**1a**) with phenylmethanol (**2f**) leading to 3-(benzyloxy)-*N*-phenylpropanamide (**3f**) was used as the model to optimize conditions including the catalysts, bases, solvents and temperature without extrusion of air. As shown in Table 1, four bases were tested using 10 mol% $CuCl_2$ as the catalyst, $CH_2Cl_2$ as the solvent under reflux (39 °C) (entries 1–4), and $Cs_2CO_3$ provided the highest yield (entry 1). Only trace amount of product was observed in the absence of base (entry 5). Yields decreased when the amount of base was reduced (entries 6 and 7). The effect of solvents was investigated (compare entries 1 and 8–11), and $CH_2Cl_2$ was the most suitable (entry 1). Other copper salts were screened (entries 12–16), and they were inferior to $CuCl_2$. Only 23% yield was afforded in the absence of the copper-catalyst (entry 17).

**Table 1** Copper-catalyzed Michael addition of *N*-phenylacrylamide (**1a**) with phenylmethanol (**2f**) leading to 3-(benzyloxy)-*N*-phenylpropanamide (**3f**): optimization of conditions[a]



| Entry | Cat. | Base (equiv.) | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $CuCl_2$ | $Cs_2CO_3$ (1) | $CH_2Cl_2$ | 78 |
| 2 | $CuCl_2$ | $K_2CO_3$ (1) | $CH_2Cl_2$ | 52 |
| 3 | $CuCl_2$ | $K_3PO_4$ (1) | $CH_2Cl_2$ | 76 |
| 4 | $CuCl_2$ | $KOBu^t$ (1) | $CH_2Cl_2$ | 21 |
| 5 | $CuCl_2$ | — | $CH_2Cl_2$ | Trace |
| 6 | $CuCl_2$ | $Cs_2CO_3$ (0.2) | $CH_2Cl_2$ | 18 |
| 7 | $CuCl_2$ | $Cs_2CO_3$ (0.5) | $CH_2Cl_2$ | 41 |
| 8 | $CuCl_2$ | $Cs_2CO_3$ | $ClCH_2CH_2Cl$ | 57 |
| 9 | $CuCl_2$ | $Cs_2CO_3$ | $CH_3CN$ | 8 |
| 10 | $CuCl_2$ | $Cs_2CO_3$ | Toluene | 36 |
| 11 | $CuCl_2$ | $Cs_2CO_3$ | 1,4-Dioxane | 40 |
| 12 | CuCl | $Cs_2CO_3$ | $CH_2Cl_2$ | 38 |
| 13 | CuBr | $Cs_2CO_3$ | $CH_2Cl_2$ | 33 |
| 14 | CuI | $Cs_2CO_3$ | $CH_2Cl_2$ | 50 |
| 15 | $Cu(OAc)_2$ | $Cs_2CO_3$ | $CH_2Cl_2$ | 20 |
| 16 | $CuSO_4$ | $Cs_2CO_3$ | $CH_2Cl_2$ | 28 |
| 17 | — | $Cs_2CO_3$ | $CH_2Cl_2$ | 23 |
| **18** | $\mathbf{CuCl_2}$ | $\mathbf{Cs_2CO_3}$ | $\mathbf{CH_2Cl_2}$ | **82**[c] |
| 19 | $CuCl_2$ | $Cs_2CO_3$ | $CH_2Cl_2$ | 55[d] |
| 20 | $CuCl_2$ | $Cs_2CO_3$ | $CH_2Cl_2$ | 38[e] |

[a] Reaction conditions: *N*-phenylacrylamide (**1a**) (0.5 mmol), phenylmethanol (**2f**) (0.5 mmol), catalyst (0.05 mmol), solvent (1.0 mL) under reflux, reaction time (12 h). [b] Isolated yield. [c] Phenylmethanol (**2a**) (1.0 mmol). [d] Reaction temperature (25 °C). [e] Catalyst (0.025 mmol).

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† Electronic supplementary information (ESI) available: General procedure for synthesis, characterization data, and $^1H$ and $^{13}C$ NMR spectra of compounds **3a–x**. See DOI: 10.1039/c2cc37595h

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The yield increased from 78% to 82% when 2 equiv. of phenylmethanol (**2a**) was used as the partner of *N*-phenylacrylamide (**1a**). The reaction provided 55% yield when it was carried out at room temperature (25 °C). When 5 mol% $CuCl_2$ was used as the catalyst, the yield decreased to 38% (entry 20). Therefore, the optimized copper-catalyzed conditions are as follows: 10 mol% $CuCl_2$ as the catalyst, one equiv. of $Cs_2CO_3$ as the base, $CH_2Cl_2$ as the solvent at 39 °C without extrusion of air.

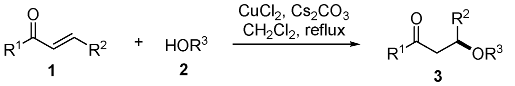
With the optimized copper-catalyzed conditions in hand, the scope for Michael addition of acrylic derivatives with primary alcohols was investigated. As shown in Table 2, the examined substrates provided moderate to excellent yields. For substituted acrylamides (**1a–h**), their reactivity was affected by steric hindrance and electronic effect of the substrates. The substrates containing bigger groups and higher electronic density exhibited lower reactivity. A stronger base, $CH_3ONa$, was required for the reaction of (*E*)-*N*-phenylhex-2-enamide (**1f**) with $CH_3OH$ (entry 18), and 1-(piperidin-1-yl)prop-2-en-1-one (**1g**) gave lower yield (48%) under the standard conditions (entry 19). For acrylic esters (**1i** and **1j**), the Michael addition afforded higher yields (entries 21–23). Unfortunately, the ester bonds were hydrolyzed into the corresponding acids because of addition of water from the solvent and reagents. For primary alcohols, steric hindrance was a key factor. For example octan-1-ol (**2d**) gave lower yield (entry 4). The reactions could tolerate some functional groups including amide bond (entries 1–20), $CF_3$ (entry 5), ether (entry 8), C–Br bond (entry 9), nitro (entry 10), alkenyl (entry 11), alkyne group (entry 12) and oxygen heterocycle (entry 13) in the substrates.

According to the above results, a possible mechanism for copper-catalyzed Michael addition of acrylic derivatives with primary alcohols in the presence of base is proposed in Scheme 1. Treatment of primary alcohol (**2**) with $CuCl_2$ in the presence of $Cs_2CO_3$ provides **I**, and coordination of **I** with **1** leads to **II**.[11] Michael addition of the alkoxyl anion to the acrylic derivative provides **III**, and reaction of **III** with **2** gives **IV** leaving the copper catalyst–alkoxyl complex **I** that enters the catalytic cycle again. Finally, isomerization of **IV** affords the target product (**3**).

We attempted the copper-catalyzed Michael addition of (*E*)-but-2-enenitrile (**1k**) with phenylmethanol (**2f**) under the standard conditions, and the corresponding product (**3x**) was obtained in 96% yield (Scheme 2). Therefore, the present method can be used in the Michael addition of other alkenes containing α-electron-withdrawing groups.

In conclusion, we have developed an easy and efficient copper-catalyzed Michael addition of acrylic derivatives with primary alcohols in the presence of base. The protocol uses readily available acrylic derivatives and primary alcohols as the starting materials, $CuCl_2$ as the catalyst, $Cs_2CO_3$ as the base, and $CH_2Cl_2$ as the solvent, the reactions were performed well under mild conditions without extrusion of air, and the corresponding addition products with carbon–oxygen bonds were obtained in moderate to excellent yields. The method could tolerate some functional groups in the substrates. This is the first example for copper-catalyzed Michael addition with weak primary alcohols thus far. Therefore, the present method will find wide applications in various fields.

**Table 2** Copper-catalyzed Michael addition of acrylic derivatives with primary alcohols[a]



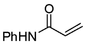
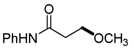
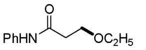
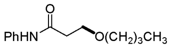
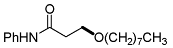
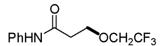
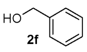
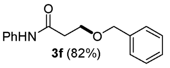
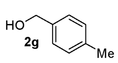
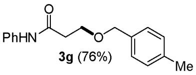
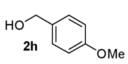
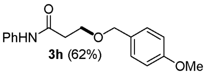
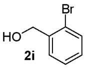
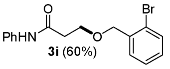
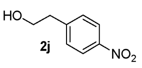
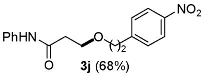
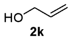
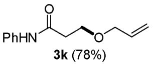
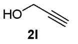
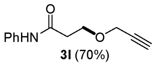
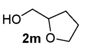
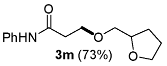
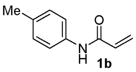
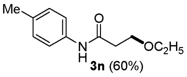
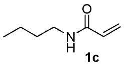
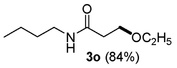
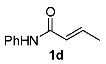
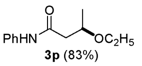
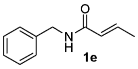
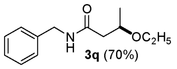
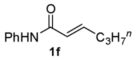
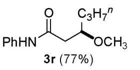
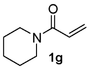
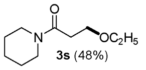
| Entry | 1 | 2 | 3 (Yield[b]) |
|---|---|---|---|
| 1 |  1a | $CH_3OH$ 2a |  3a (89%) |
| 2 | **1a** | $CH_3CH_2OH$ 2b |  3b (88%) |
| 3 | **1a** | $CH_3(CH_2)_3OH$ 2c |  3c (58%) |
| 4 | **1a** | $CH_3(CH_2)_7OH$ 2d |  3d (37%) |
| 5 | **1a** | $CF_3CH_2OH$ 2e |  3e (86%) |
| 6 | **1a** |  2f |  3f (82%) |
| 7 | **1a** |  2g |  3g (76%) |
| 8 | **1a** |  2h |  3h (62%) |
| 9 | **1a** |  2i |  3i (60%) |
| 10 | **1a** |  2j |  3j (68%) |
| 11 | **1a** |  2k |  3k (78%) |
| 12 | **1a** |  2l |  3l (70%) |
| 13 | **1a** |  2m |  3m (73%) |
| 14 |  1b | **2b** |  3n (60%) |
| 15 |  1c | **2b** |  3o (84%) |
| 16 |  1d | **2b** |  3p (83%) |
| 17[c] |  1e | **2b** |  3q (70%) |
| 18[d] |  1f | **2a** |  3r (77%) |
| 19 |  1g | **2b** |  3s (48%) |

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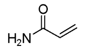
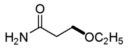
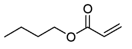
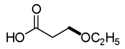
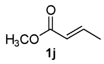
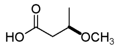
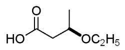
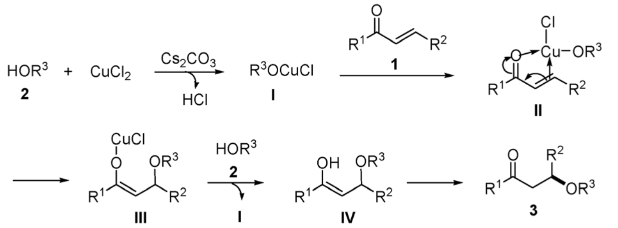
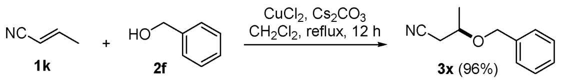
**Table 2** (*continued*)

| Entry | **1** | **2** | **3** (Yield[b]) |
|---|---|---|---|
| 20 |  **1h** | **2b** |  **3t** (94%) |
| 21 |  **1i** | **2b** |  **3u** (85%) |
| 22 |  **1j** | **2a** |  **3v** (75%) |
| 23 | **1j** | **2b** |  **3w** (73%) |

[a] Reaction conditions: **1** (2.0 mmol), **2** (4.0 mmol), $CuCl_2$ (0.2 mmol), $Cs_2CO_3$ (2.0 mmol), $CH_2Cl_2$ (4.0 mL) under reflux, reaction time (12 h). [b] Isolated yield. [c] Under a nitrogen atmosphere. [d] $CH_3ONa$ (2.0 mmol) as the base, $CH_3OH$ (4.0 mL) as the solvent under reflux.



**Scheme 1** A possible mechanism for copper-catalyzed Michael addition of acrylic derivatives with primary alcohols.



**Scheme 2** Copper-catalyzed Michael addition of (*E*)-but-2-enenitrile (**1k**) with phenylmethanol (**2f**).

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