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# Copper-catalyzed tandem reaction of 2-bromobenzyl bromides with 1,3-dicarbonyl compounds leading to 4*H*-chromenes

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**Abstract**

A Cu(I)-catalyzed one-pot tandem reaction of 2-bromobenzyl bromides with 1,3-dicarbonyl compounds leading to 4*H*-chromene derivatives has been developed. This new approach toward 4*H*-chromenes combines several reactions in one pot and builds molecular complexity from readily available starting materials.



*Keywords:* One-pot tandem reaction; 4*H*-Chromenes; Copper catalysis

Tandem reactions are emerging as a powerful tool for organic chemists. Compared with classical organic synthesis involving stepwise formation of individual bonds in the construction of a targeted molecule, tandem reactions combine multiple transformations in one pot and allow rapid buildup of molecular complexity from relatively simple starting materials. In addition, this kind of reaction not only saves time and energy, but also reduces the use of solvents in the isolation and purification of intermediates [1].

Chromenes constitute a widespread structural motif in various biologically active compounds and naturally occurring products [2]. Compounds bearing a 4*H*-chromene moiety have showed remarkable biological activities [3]. Due to their importance, several methods for the synthesis of 4*H*-chromenes have been developed [4–9]. Li *et al.* have recently reported a synthesis of 4*H*-chromene derivatives starting from 2-bromobenzyl bromides and 1,3-dicarbonyl compounds [10]. However, Li's synthesis of 4*H*-chromenes combines two separate steps and the first step is unfortunately very low yielding (Scheme 1) [11]. As a continuation of our research interest in tandem reactions [12], we were interested in developing an efficient and practical approach to 4*H*-chromenes directly from 2-bromobenzyl bromides and 1,3-dicarbonyl compounds *via* a one-pot tandem procedure (Scheme 1) [13].

Initially, we chose 2-bromobenzyl bromide (**1a**, 0.5 mmol) and cyclohexane-1,3-dione (**2a**, 1.0 mmol) as substrates for surveying the reaction parameters. **1a** and **2a** were firstly treated with CuI and $Cs_2CO_3$ in dioxane in the presence of *N,N*'-dimethyl ethylenediamine (DMEDA) at reflux for 12 h. From the reaction mixture, the expected **3a** was isolated but in a low yield (21%). The reaction was then tried under different conditions with regard to different bases, solvents,

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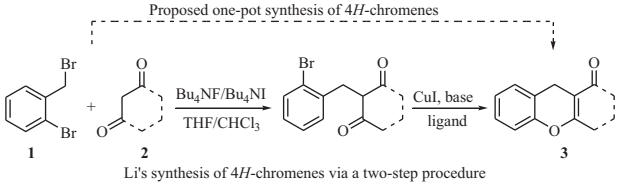



Scheme 1. Li's synthesis of 4*H*-chromenes *via* a two-step procedure.

and Cu sources. It turned out that $K_2CO_3$ was as effective as $Cs_2CO_3$. Next, we found the nature of solvent was essential to influence the yield. Among the solvents studied (dioxane, *i*-PrOH, DMF, DMSO, THF), *i*-PrOH was ineffective, whereas DMF gave the best results. Then, several ligands such as pipecolinic acid, *N,N*-dimethyl glycine and *L*-proline were tried and they did not give better yields of **3a** than DMEDA, which gave **3a** in a yield of 57%. To our surprise, a control experiment without using any ligand afforded **3a** in a yield of 58%. However, when the amount of **2a** was reduced from 2 equiv to 1 equiv, the yield of **3a** decreased dramatically, indicating that **2a** may act as a ligand in this tandem process. With regard to Cu source, CuBr, CuCl and CuCN were inferior to CuI in promoting this reaction. The effect of catalyst loading was also examined. When the amount of CuI was increased to 20 mol% from 10 mol%, the yield of **3a** did not improve substantially. Furthermore, the cascade reaction gave poor yields of **3a** when the temperature was below 100 °C. Based on the above results, the optimal conditions were identified as follows: **1a** (0.5 mmol), **2a** (1.0 mmol), CuI (0.05 mmol), $K_2CO_3$ (1.5 mmol), in DMF at 100 °C for 12 h. Under such conditions, **3a** was obtained in a yield of 58%.

With the optimized reaction conditions in hand, the scope of this one-pot synthesis of 4*H*-chromenes was studied. For this purpose, several 5-alkyl or 5-aryl substituted cyclohexane-1,3-diones (**2b–2f**) were prepared and reacted smoothly with **1a** (Table 1, entries 2–6). Next, we found it was well compatible with 1-bromo-2-(bromomethyl)-naphthalene (**1b**) (entries 7 and 8). In addition, reactions with 5-bromo-6-(bromomethyl)-benzo[*d*][1,3]dioxole (**1c**) gave the corresponding 4*H*-chromenes in moderate yields (entries 9 and 10). Interestingly, in addition to cyclic 1,3-diketones, an acyclic 1,3-diketone, 1,3-diphenylpropane-1,3-dione (**2g**), took part in this tandem process smoothly (entries 11–13).

Table 1
Preparation of 4*H*-chromenes **3** [a] [14].

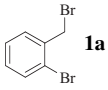
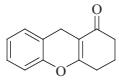
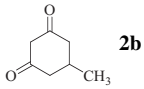
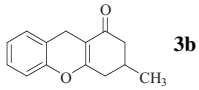
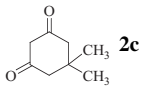
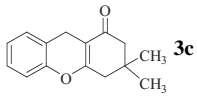
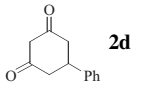
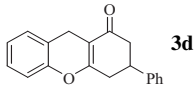
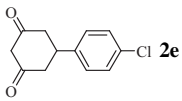
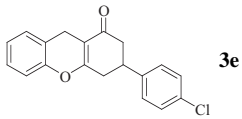
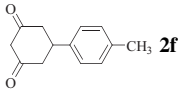
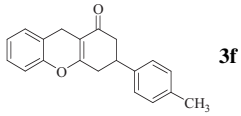
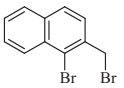
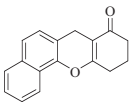
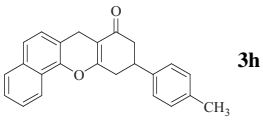
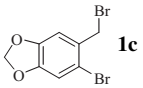
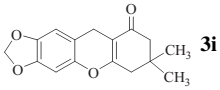
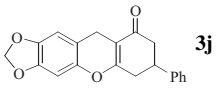
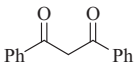
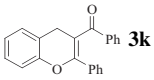
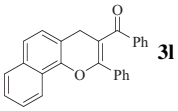
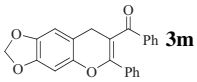
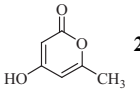
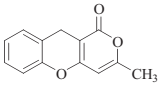
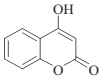
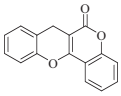
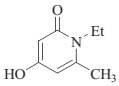
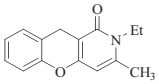
| Entry | 1 | 2 | 3 | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | 58 |
| 2 | **1a** |  **2b** |  **3b** | 54 |
| 3 | **1a** |  **2c** |  **3c** | 58 |
| 4 | **1a** |  **2d** |  **3d** | 45 |
| 5 | **1a** |  **2e** |  **3e** | 41 |
| 6 | **1a** |  **2f** |  **3f** | 46 |

Table 1 (*Continued*)

| Entry | 1 | 2 | 3 | Yield (%)[b] |
|---|---|---|---|---|
| 7 |  **1b** | **2a** |  **3g** | 55 |
| 8 | **1b** | **2f** |  **3h** | 53 |
| 9 |  **1c** | **2c** |  **3i** | 57 |
| 10 | **1c** | **2d** |  **3j** | 49 |
| 11 | **1a** |  **2g** |  **3k** | 45 |
| 12 | **1b** | **2g** |  **3l** | 44 |
| 13 | **1c** | **2g** |  **3m** | 42 |
| 14 | **1a** |  **2h** |  **3n** | 46 |
| 15 | **1a** |  **2i** |  **3o** | 37 |
| 16 | **1a** |  **2j** |  **3p** | 38 |

[a] 0.5 mmol of **1**, 1.0 mmol of **2**, 0.05 mmol of CuI, 1.5 mmol of $K_2CO_3$, 3 mL of DMF, 100 °C, 12 h.
[b] Isolated yields.

Finally, the applicability of 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2h**), 4-hydroxy-2*H*-chromen-2-one (**2i**), and 4-hydroxy-6-methyl-pyridine-2(*1H*)-one (**2j**) for this tandem process was also studied. Under standard conditions, the reactions of **2h**–**2j** with **1a** proceeded smoothly to give the corresponding products **3n**, **3o**, and **3p** in 46%, 37%, and 38% yields, respectively (Table 1, entries 14–16), thus resulting a promising approach toward the biologically interesting chromenopyranones and chromenopyridinones.

In summary, we have successfully developed a novel synthesis of 4*H*-chromene derivatives through CuI-catalyzed one-pot tandem reaction of various 1,3-dicarbonyl compounds with 2-bromobenzyl bromides under ligand free conditions. The choices of solvent and base are essential to the success of this tandem process. Compared with literature methods, advantages of the present protocol include readily available starting materials, free of added ligands, simple operation process, and reasonably good yields.

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[14] Typical procedure for the preparation of **3a**: To a solution of 2-bromobenzyl bromide (**1a**, 0.5 mmol) and cyclohexane-1,3-dione (**2a**, 1.0 mmol) in DMF (3 mL) were added $K_2CO_3$ (1.5 mmol) and CuI (0.05 mmol). The mixture was stirred at 100 °C until a complete conversion. It was cooled to room temperature and added with water, then extracted with ethyl ether (5 mL × 3). The combined organic phases were concentrated under vacuum. The crude product was purified by column chromatography eluting with ethyl acetate/hexane (10–20%) to give the desired product **3a**. Products **3b**–**3p** were obtained in a similar manner. **3a**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.00–2.06 (m, 2H), 2.44 (t, 2H, $J$ = 6.4 Hz), 2.53 (t, 2H, $J$ = 6.4 Hz), 3.48 (s, 2H), 6.93 (d, 1H, $J$ = 7.6 Hz), 7.03 (t, 1H, $J$ = 6.8 Hz), 7.11–7.15 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.6, 21.1, 27.7, 36.6, 109.9, 116.4, 120.8, 124.6, 127.6, 129.7, 149.7, 166.8, 198.1. MS: $m/z$ 201 $(MH)^+$. HRMS (FAB) Calcd. for $C_{13}H_{13}O_2$: 201.0916 [M+H], found: 201.0919.