Synthesis of 3-Substituted Isocoumarin Derivatives via CuI-Catalyzed Reaction of *o*-Bromobenzamides with 1,3-Diketones

Shangjun Cai, Fei Wang, Chanjuan Xi*

Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. of China
E-mail: cjxi@tsinghua.edu.cn

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Abstract: An approach to a variety of 3-substituted isocoumarins has been developed. The reaction proceeded from *o*-bromobenzamide derivatives and 1,3-diketones via CuI-catalyzed reaction in DMF under the action of K_3PO_4 at 120 °C without ligands or additives.

Key words: copper, domino reaction, isocoumarins, *o*-bromobenzamides, 1,3-diketones

Heterocycles are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. As a consequence, the ongoing interest for developing new, versatile, and efficient syntheses of heterocycles has always been an important task for the synthetic community. Among a variety of new synthetic transformations, transition metal-catalyzed reactions are some of the most attractive methodologies for synthesizing heterocyclic compounds, since a transition metal-catalyzed reaction can directly construct complicated molecules from readily accessible starting materials under mild conditions.[1] A recent advance in copper-catalyzed reactions provided the opportunity for the development of new methodologies to assemble heterocycles.[2] For example, Ma et al. and Bao et al. had developed Cu-catalyzed domino process for elaboration of heterocycles such as indoles,[2e,m] isoquinolines,[2p] and quinoxalin-2(1*H*)-ones.[2q] Our group has recently established some domino processes for elaboration of heterocycles via Cu-catalyzed addition/cyclization or coupling/cyclization reactions, which included formation of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one,[3] 2-aminobenzimidazoles,[4] thiophenes,[5] and pyrroles.[6] As part of an ongoing program in our laboratory to systematically synthesize a variety of heterocyclic compounds action in a one-pot strategy, we found that Cu-catalyzed reaction of *o*-halobenzoic acids with 1,3-diketones afforded 3-substituted isocoumarins,[7] which are ubiquitous structural units in natural products with biological interests.[8] Fan and co-workers reported that Cu-catalyzed tandem reaction of *o*-bromobenzoates with acyclic 1,3-diones also afforded 3-substituted isocoumarins.[9] Encouraged by these results, we envisioned that Cu-catalyzed reaction of *o*-bromobenzamides with acyclic 1,3-diones could afford isoquinolinone derivatives, which are versatile building blocks in a wide variety of plant alkaloids[10] and in pharmacological compounds.[11] During the course of our investigations, we obtained the 3-substituted isocoumarin rather than the expected isoquinolinones. Herein, we would like to report CuI-catalyzed reaction of *o*-bromobenzamide and 1,3-diketones to synthesize 3-substituted isocoumarins.

Initially, *o*-bromobenzamide (**1a**) and pentane-2,4-dione (**2a**) were used as the model substrates for the optimization of the reaction conditions. The results are summarized in Table 1. Substrates **1a** and **2a** were first subjected to the following typical conditions: CuI, 10 mol%; solvent, toluene; and base, Cs_2CO_3 at 120 °C to afford 3-methyl-1*H*-isochromen-1-one (**3a**) in 20% yield after 24 hours (Table 1, entry 1). Other bases were also evaluated in the reaction (entries 2–5). Among the bases screened, K_3PO_4 proved to be superior. Then, different solvents such as MeCN, *N*-methyl-2-pyrrolidone (NMP), DMF, and DMSO were screened (entries 2, 6–9). To our delight, DMF was found to be efficient and the yield of product increased to 70% (entry 8). Prolonging the reaction time to 48 hours did not help to improve yield of **3a** (entry 10). Usually, ligands play an important role in the copper-catalyzed coupling reactions, thus several ligands were screened (entries 11–13). Surprisingly, all the ligands screened did not help the reaction, in other words, the reaction did not need ligand or additive. The reaction also showed a strong dependence on temperature. Thus, the reaction did not proceed at 80 °C (entry 14), but on heating the reaction mixture to 110 °C, the desired product was formed in 60% yield (entry 15). At a still higher temperature of 130 °C, the desired product was formed in 69% yield (entry 16). On the other hand, the reaction did not take place at all in the absence of CuI (entry 17). Based on these results, the optimal conditions involved the following ligand-free parameters: CuI as catalyst, K_3PO_4 as base, and DMF as solvent, at 120 °C. Furthermore, since the unexpected isocoumarin was obtained in the reaction, we carefully authenticated product **3a** by elemental analyses, solution NMR, and melting point. All the data showed that the isocoumarin had formed.

Under these optimized conditions, a study on the substrate scope has been carried out, and the results are summarized in Table 2. At first, *o*-bromobenzamide **1a** was used to react with various 1,3-diketones. Both pentane-2,4-dione (**2a**) and heptane-3,5-dione (**2b**) showed good performance (Table 2, entries 1, 2). The reaction of **1a** with 1,3-

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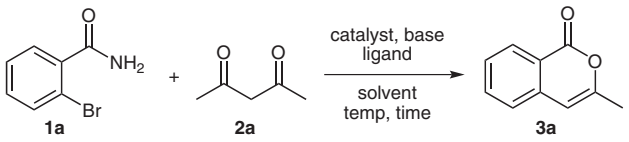
Table 1 Optimization of the Reaction between *o*-Bromobenzamide and Pentane-2,4-dione[a]



Entry	Base	Ligand	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	Cs_2CO_3	–	toluene	120	24	20
2	K_3PO_4	–	toluene	120	24	54
3	*t*-BuONa	–	toluene	120	24	n.r.
4	DBU	–	toluene	120	24	33
5	DABCO	–	toluene	120	24	27
6	K_3PO_4	–	MeCN	120	24	31
7	K_3PO_4	–	NMP	120	24	51
8	K_3PO_4	–	DMF	120	24	70
9	K_3PO_4	–	DMSO	120	24	65
10	K_3PO_4	–	DMF	120	48	71
11	K_3PO_4	proline	DMF	120	24	32
12	K_3PO_4	DMEDA	DMF	120	24	67
13	K_3PO_4	1,10-phenanthroline	DMF	120	24	31
14	K_3PO_4	–	DMF	80	24	n.r.
15	K_3PO_4	–	DMF	110	24	60
16	K_3PO_4	–	DMF	130	24	69
17[c]	K_3PO_4	–	DMF	120	24	n.r.

[a] Unless otherwise noted, the reaction was performed with **1a** (0.5 mmol), **2a** (0.5 mmol), CuI (0.05 mmol), and base (1 mmol) in solvent (1 mL) under N_2.
[b] Isolated yield; n.r. = no reaction.
[c] Without CuI.

diphenylpropane-1,3-dione (**2c**) did not proceed even by heating the reaction to 130 °C for 48 hours (entry 3). When unsymmetrical 1,3-diketone **2d** was engaged in the system, the reaction regioselectively gave one product **3c** in 32% yield (entry 4). Other substituted *o*-bromobenzamide derivatives were then applied under the optimized conditions. In most cases, the reaction with *o*-bromobenzamide derivatives could proceed smoothly and the products were obtained in satisfactory yields. For example, when **1b** or **1c** was treated with **2a** under the optimized conditions, the desired product was obtained in 62% or 71% yield, respectively (entries 5, 6). When 2-bromo-5-methoxybenzamide (**1d**) was employed as the substrate, the desired product was formed only in 24% yield (entry 7). Reaction of **1c** with **2b** afforded the product **3h** in 64% yield (entry 9). To our delight, the product **3h** was suitable for single crystal analysis, and its structure was fully characterized by X-ray diffraction analysis.[12] The structure of **3h** is shown in Figure 1 with some corresponding bond lengths and angles. It clearly shows the formation of isocoumarin in the reaction. When 2-bromo-4-fluorobenzamide (**1e**) was treated with **2a** the product **3i** was obtained in lower yield (entry 10); most of the starting materials remained, which may be attributed to electron deficiency on the benzene ring of *o*-bromobenzamide. A substrate with two substituents situated *para* and *meta* to the acylamino group also afforded an good yield of the corresponding products (entries 11 and 12). When N-substituted *o*-bromobenzamides were employed in the reaction, isocoumarin **3a** was obtained again (entries 13,14).

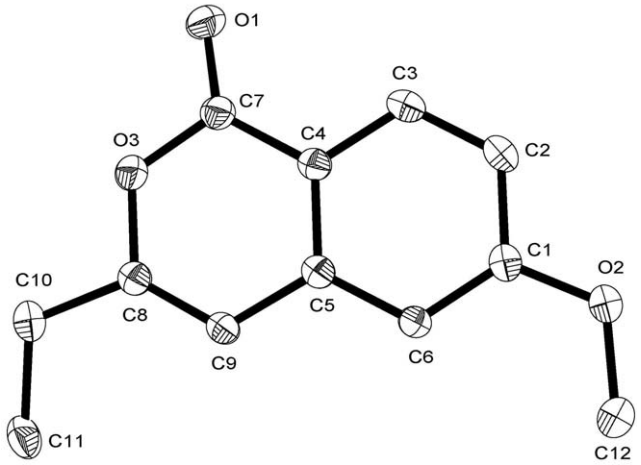
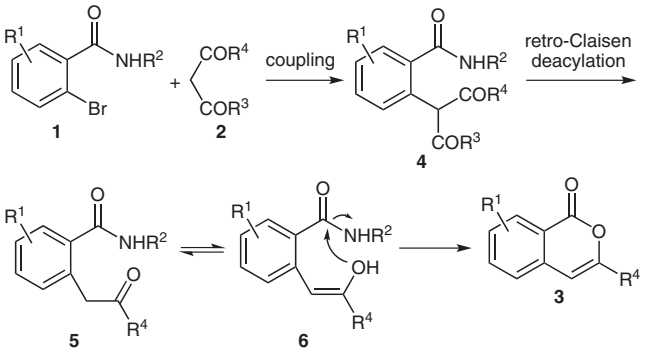


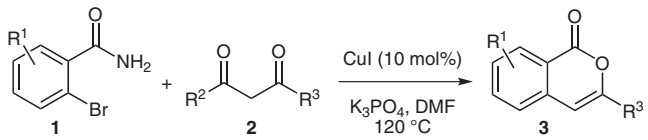
Figure 1 Structure of **3h**. Selected bond lengths (Å) and angles (°): O3–C7, 1.382(3); O3–C8, 1.389(3); C7–O3–C8, 122.19(17); C9–Cb–O3, 121.57(19); O3–C7–C4, 117.09(18).

Although there is little experimental evidence at present to determine the exact reaction pathway for the cascade sequence process, the following three steps are believed to play some part in the reaction (Scheme 1): (i) coupling reaction,[13] (ii) retro-Claisen deacylation to give intermediate **5**,[14] and (iii) an intramolecular lactonization with loss of an amine.



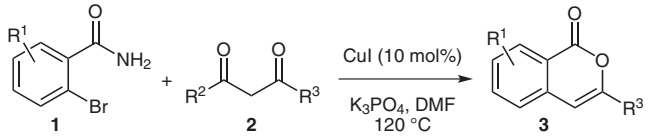
Scheme 1 Possible reaction pathway for the formation of 3-substituted isocoumarins

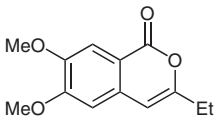
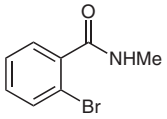
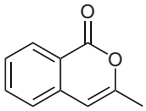
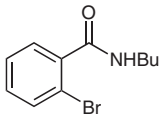
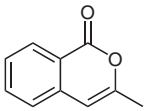
Table 2 Reaction of *o*-Bromobenzamides with 1,3-Diketones[a]



Entry	Substrate **1**	Substrate **2**	Time (h)	Product	Yield (%)[b]
1	**1a**	**2a**	24	**3a**	65
2	**1a**	**2b**	24	**3b**	57
3	**1a**	**2c**	48	**3c**	n.r.
4	**1a**	**2d**	24	**3c**	32
5	**1b**	**2a**	24	**3d**	62
6	**1c**	**2a**	24	**3e**	71
7	**1d**	**2a**	48	**3f**	24
8	**1b**	**2b**	24	**3g**	48
9	**1c**	**2b**	24	**3h**	64
10	**1e**	**2a**	48	**3i**	trace
11	**1f**	**2a**	24	**3j**	66

Table 2 Reaction of *o*-Bromobenzamides with 1,3-Diketones[a] (continued)



Entry	Substrate **1**	Substrate **2**	Time (h)	Product	Yield (%)[b]
12	**1f**	**2b**	24	**3k** 	59
13	**1g** 	**2a**	24	**3a** 	55
14	**1h** 	**2a**	24	**3a** 	52

[a] Unless otherwise noted, the reaction was performed with **1** (0.5 mmol), **2** (0.5 mmol), CuI (0.05 mmol), and K_3PO_4 (1 mmol) in DMF (1 mL) under N_2 for 24 h.
[b] Isolated yield; n.r. = no reaction.

In conclusion, we have demonstrated a new method based on CuI-catalyzed domino process for the construction of 3-substituted isocoumarins from *o*-bromobenzamides and 1,3-diketones. The reaction of *o*-bromobenzamides with 1,3-diketones was performed well without addition of any ligand or additive. Considering the relatively inexpensive catalytic system and the commercial availability of the starting materials, it should be of great benefit in organic synthesis.

All the reactions were carried out in a predried screw-capped tube with a Teflon-lined septum under N_2 atmosphere. Unless otherwise indicated, all materials were obtained from commercial sources and used as received. DMF, toluene, MeCN, and DMSO were freshly distilled. Column chromatography was performed on silica gel (particle size 10–40 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 MHz and 600 MHz spectrometer at r.t. with DMSO-d_6 and $CDCl_3$ as the solvent.

3-Substituted Isocoumarins 3; General Procedure
A sealed tube was charged with a mixture of *o*-bromobenzamide **1** (0.5 mmol), 1,3-diketone **2** (0.5 mmol), CuI (0.05 mmol, 10 mg), and K_3PO_4 (1.0 mmol, 212 mg) in DMF (1 mL) and the reaction mixture was stirred at r.t. under N_2 atmosphere. Half an hour later, the tube was sealed and the mixture was allowed to stir at 120 °C for the indicated time (Table 2). After completion, the mixture was cooled to r.t., then H_2O (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4). Evaporation of the solvent followed by purification of the residue on silica gel [petroleum ether (bp 60–90 °C)–EtOAc, 5:1] provided the desired product (Table 2).

3-Methyl-1*H*-isochromen-1-one (3a)[15]
Yield: 51 mg (65%); white solid; mp 68–70 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.16 (s, 3 H), 6.40 (s, 1 H), 7.42 (q, $J_{H,H}$ = 14.4 Hz, 2 H), 7.70 (t, $J_{H,H}$ = 7.2 Hz, 1 H), 8.02 (d, $J_{H,H}$ = 7.6 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.0, 103.2, 119.1, 125.2, 127.6, 128.6, 135.0, 137.3, 154.4, 161.9.

ESI-MS: *m*/*z* = 161.4 $[M + H]^+$.

Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.89; H, 5.06.

3-Ethyl-1*H*-isochromen-1-one (3b)[15]
Yield: 49 mg (57%); white solid; mp 70–72 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, $J_{H,H}$ = 7.6 Hz, 3 H), 2.57 (q, $J_{H,H}$ = 14.4 Hz, 2 H), 6.25 (s, 1 H), 7.36 (d, $J_{H,H}$ = 7.9 Hz, 1 H), 7.45 (t, $J_{H,H}$ = 7.2 Hz, 1 H), 7.67 (t, $J_{H,H}$ = 7.6 Hz, 1 H), 8.25 (d, $J_{H,H}$ = 7.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 26.8, 102.1, 120.3, 125.2, 127.7, 129.7, 134.8, 137.8, 159.7, 163.2.

ESI-MS: *m*/*z* = 175.3 $[M + H]^+$.

3-Phenyl-1*H*-isochromen-1-one (3c)[15]
Yield: 35 mg (32%); white solid; mp 85–87 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.45–7.59 (m, 5 H), 7.66–7.68 (m, 1 H), 7.80–7.92 (m, 3 H), 8.12–8.15 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 102.1, 119.8, 124.9, 126.6, 128.6, 128.9, 129.0, 130.0, 131.6, 135.4, 137.3, 152.4, 161.3.

ESI-MS: *m*/*z* = 223.2 $[M + H]^+$.

3,6-Dimethyl-1*H*-isochromen-1-one (3d)[7]
Yield: 53 mg (62%); white solid; mp 68–70 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.22 (s, 3 H), 2.41 (s, 3 H), 6.46 (s, 1 H), 7.32 (d, $J_{H,H}$ = 11.7 Hz, 2 H), 7.96 (d, $J_{H,H}$ = 8.3 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.1, 21.4, 103.1, 116.7, 125.1, 128.7, 129.0, 137.5, 145.8, 154.5, 161.9.

ESI-MS: *m*/*z* = 175.3 $[M + H]^+$.

6-Methoxy-3-methyl-1*H*-isochromen-1-one (3e)[16]
Yield: 67 mg (71%); white solid; mp 93–95 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.20 (s, 3 H), 3.86 (s, 3 H), 6.45 (s, 1 H), 6.98 (s, 1 H), 7.04 (d, $J_{H,H}$ = 8.6 Hz, 1 H), 7.98 (d, $J_{H,H}$ = 8.6 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.2, 55.8, 103.3, 107.5, 112.2, 116.2, 131.0, 140.0, 155.1, 161.7, 164.5.

ESI-MS: m/z = 191.3 $[M + H]^+$.

7-Methoxy-3-methyl-1*H*-isochromen-1-one (3f)[7]
Yield: 23 mg (24%); white solid; mp 99–101 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.21 (s, 3 H), 3.84 (s, 3 H), 6.49 (s, 1 H), 7.36–7.40 (m, 1 H), 7.45 (s, 1 H), 7.48 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.9, 55.6, 102.9, 109.7, 120.3, 124.1, 127.1, 131.1, 152.2, 158.7, 162.0.

ESI-MS: m/z = 191.3 $[M + Na]^+$.

3-Ethyl-6-methyl-1*H*-isochromen-1-one (3g)[7]
Yield: 45 mg (48%); white solid; mp 60–62 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.12 (t, $J_{H,H}$ = 7.5 Hz, 3 H), 2.36 (s, 3 H), 2.43–2.50 (m, 2 H), 6.41 (s, 1 H), 7.28 (d, $J_{H,H}$ = 4.1 Hz, 2 H), 7.91 (d, $J_{H,H}$ = 8.6 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.0, 21.4, 25.8, 101.6, 116.9, 125.3, 128.7, 129.1, 137.4, 145.8, 159.1, 161.8.

ESI-MS: m/z = 189.1 $[M + H]^+$.

3-Ethyl-6-methoxy-1*H*-isochromen-1-one (3h)[16]
Yield: 65 mg (64%); white solid; mp 94–95 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.19 (t, $J_{H,H}$ =7.6 Hz, 3 H), 2.50–2.54 (m, 2 H), 3.88 (s, 3 H), 6.47 (s, 1 H), 7.04–7.08 (m, 2 H), 8.00 (d, $J_{H,H}$ = 8.2 Hz, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 10.9, 25.9, 55.7, 101.7, 107.7, 112.3, 116.2, 130.9, 139.8, 159.6, 161.5, 164.4.

ESI-MS: m/z = 205.4 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.67; H, 5.98.

6,7-Dimethoxy-3-methyl-1*H*-isochromen-1-one (3j)[17]
Yield: 72 mg (66%); white solid; mp 135–137 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.21 (s, 3 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 6.42 (s, 1 H), 7.02 (s, 1 H), 7.40 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.1, 55.6, 56.0, 103.0, 106.5, 108.6, 111.8, 133.1, 148.9, 153.1, 155.0, 161.7.

ESI-MS: m/z = 221.2 $[M + H]^+$.

3-Ethyl-6,7-dimethoxy-1*H*-isochromen-1-one (3k)
Yield: 69 mg (59%); white solid; mp 168–170 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.17 (t, $J_{H,H}$ =7.6 Hz, 3 H), 2.51 (q, $J_{H,H}$ =14.4 Hz, 2 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 6.43 (s, 1 H), 7.07 (s, 1 H), 7.42 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.0, 25.8, 55.7, 56.0, 101.5, 106.7, 108.6, 112.0, 133.1, 148.9, 155.0, 157.7, 161.7.

ESI-MS: m/z = 235.3 $[M + H]^+$.

HRMS: m/z calcd for $C_{13}H_{14}O_4$: 234.0892; found: 234.0891.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are copies of spectra of compound **3a**–**h**, **3j**–**k** and CIF (X-ray data) of **3h**.

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(12) Compound **3h**: $C_{12}H_{12}O_3$, crystallized in monoclinic, space group P2(1)/c with cell parameters: a = 7.8837 (16), b = 14.156 (3), c = 18.850(4)Å3, α = 90.00, β = 98.14(3), γ = 90.00°, V = 2082.5 (7) Å3, Z = 8. CCDC-866537 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336 033; E-mail: deposit@ccdc.cam.ac.uk.

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