Copper-Catalyzed 6-endo-dig O-Cyclization of 2-(But-3-en-1-yn-1-yl)benzamide

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Abstract The copper-catalyzed synthesis of 3-vinylisocoumarin-1-imine is reported. The transformation proceeds smoothly with good yields in THF and the regioselectivity was determined by a O-nucleophilic 6-endo cyclization. Studies on the mechanism indicate that copper trifluoroacetate serves as a Lewis acid, and the use of vinyl-connected 2-alkynylbenzamide is important for this O-nucleophilic 6-endo cyclization.

Key words copper catalysis, O-nucleophilic 6-endo cyclization, Lewis acid, vinyl-connected 2-alkynylbenzamide, isocoumarin

As a dual-functionalized synthon, 2-alkynylbenzamide has attracted increasing attention from the scientific community because of its synthetic versatility in annulative reactions. Together with an improvement in reaction efficiency, we wished to explore the selectivity of N- versus O-nucleophilicity and 6-endo versus 5-exo cyclization for 2-alkynylbenzamide-based chemistry. The N/O-nucleophilicity and 6-endo/5-exo-switch has been ascribed to the use of various reaction systems. Generally, base-mediated reactions of 2-alkynylbenzamide tend to undergo N-nucleophilic 5-exo cyclization, and electrophilic cyclization of 2-alkynylbenzamide resulted in the formation of a mixture of O-nucleophilic 5-exo cyclization and O-nucleophilic 6-endo cyclization products. Pleasingly, our recent work suggested that either an O-nucleophilic 5-exo reaction or an O-nucleophilic 6-endo reaction could be realized, respectively, when radical cyclization of 2-alkynylbenzamide was conducted.

In 2009, Liu and co-workers developed a silver-catalyzed cyclization of 2-alkynylbenzamide in which a distinctive O-nucleophilic 6-endo cyclization took place with the formation of isocoumarin-1-imine derivatives (Scheme 1a). However, it was surprising that the reaction of substrates with N-alkyl protecting groups provided isocoumarin-1-imine in good yields, and N-aryl protecting substrates were not efficient reaction partners. For examples, the reaction of N-phenyl-2-phenylethynylbenzamide provided only N-phenylisocoumarin-1-imine in a 23% yield. Subsequently, many research groups also investigated O-nucleophilic 6-endo cyclization of 2-alkynylbenzamide. To our surprise, silver salts have been used in most of the examples; other metal salt-catalyzed examples of O-nucleophilic 6-endo cyclization of 2-alkynylbenzamide remain rare. Inspired by these reports, we wanted to explore O-nucleophilic 6-endo cyclization of 2-alkynylbenzamide under other metal catalysis with a view to expanding the scope of the reaction by making it compatible with substrates bearing various N-aryl protecting groups. Considering our ongoing interest in copper catalysis and the high importance of the isocoumarin-1-imine core, in this paper we would like to report the development of a copper-catalyzed O-nucleophilic 6-endo-cyclization of 2-alkynylbenzamide 1.

A preliminary result from the copper chloride-catalyzed reaction of 2-alkynylbenzamide 1 suggested the substituent R in substrate 1 had a significant impact on the outcome of the reaction. Although the expected O-nucleophilic 6-endo cyclization took place, the yields of isocoumarin-1-imine 2 varied depending on the use of the substituent R in 2-alkynylbenzamide 1. As illustrated in Scheme 1b, the reaction of 2-phenylethynylbenzamide provided the desired product 2a in 35% yield, whereas reaction...
of 2-(but-3-en-1-yn-1-yl)benzamide gave rise to the corresponding product 2c in 77% yield without further reaction optimization. We assumed that the substituent R probably stabilized the resulting copper-involved species through a coordination effect during the process. Given the synthetic potential of the vinyl group for structural elaboration, we optimized the reaction of 2-(but-3-en-1-yn-1-yl)benzamide for the formation of 3-vinylisocoumarin-1-imines.

The optimization of the reaction is summarized in Table 1. We initially explored a range of copper sources including Cu(OAc)2, Cu(TFA)2, CuI and CuBr, and found that the use of Cu(TFA)2 greatly improved the efficiency of the reaction to deliver the desired product 2c in 90% yield (entry 3). Solvent screening suggested that tetrahydrofuran (THF) was optimal; other solvents including 1,4-dioxane, 1,2-dichloroethane (DCE), MeCN, toluene, and DMF did not deliver better yields (entries 6–10). Reducing either the reaction temperature or the copper loading had a negative impact on the outcome of the reaction (entries 11 and 12). As such, we established the optimized conditions as Cu(TFA)2 (10 mol%), THF, and 60 °C.

With the optimized conditions in hand, we then explored the scope and generality of the reaction. The results are illustrated in Scheme 2. A range of vinyl group-connected substrates were compatible with the reaction conditions. For instance, the reaction of cyclohexene-linked substrate provided the desired product 2f in a 75% yield. The screening of substituent R1 showed that this substituent could be replaced with methyl, chloro, fluoro, or bromo groups, and the corresponding products 2g–j were achieved in moderated to good yields. Interestingly, the reaction of 3-enynynaphthalen-2-amide 1k also worked well, leading to the expected isocoumarin-1-imine 2k in 78% yield. The structure of 2j was confirmed by X-ray diffraction analysis (CCDC 1941980).

Subsequently, the substituent effect of N-protecting groups was also examined. From the results, the N-protecting group could be aryl, heteroaryl, alkyl, and complex molecular blocks. For example, 6-pyridinyl-2-(but-3-en-1-yn-1-yl)benzamide was recognized as an efficient reaction partner, resulting in the formation of 6-pyridinyl-3-vinylisocoumarin-1-imine (2o) in 74% yield. Other N-alkyl group-linked substrates were also suitable for the reactions, producing the corresponding products 2p–s in 72–92% yield.

In particular, substrates with complex N-protecting groups were also compatible with the reaction. For instance, the reaction of the substrates with N-phenylalanine and N-alanine worked uniquely well, leading to the desired products 2u and 2v in 82% and 85% yields, respectively. The rosin amine-connected substrate was also a good reaction partner, producing the desired product 2w in 81% yield.

Additionally, the reaction of N-imine-2-alkynylbenzamide 1x was conducted under the standard conditions. As expected, the desired N-imineisocoumarin-1-imine 2x was achieved in moderated yield (Scheme 3).
Subsequently, structural elaboration of 3-vinylisocoumarin-1-imine 2 was investigated. The results are presented in Scheme 4. Thus, 3-vinylisocoumarin 3 was readily accessible through hydrolysis of 3-vinylisocoumarin-1-imine 2c. Moreover, 3-vinylisocoumarin 3, generated in situ, was readily converted into 1-amino-3-vinylisoquinoline 4 in good yields. To gain insights into reaction mechanism, several control experiments were carried out. As presented in Scheme 5, the first trial was to confirm the role of the copper catalyst. A control reaction with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as an additive was conducted. The use of TEMPO did not make significant impact on the reaction, indicating the role of copper catalyst as a Lewis acid. We then examined whether the vinyl group assisted in the reaction. Under standard conditions we ran the reactions of...
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The solvents were distilled from standard drying agents. Unless otherwise stated, commercial reagents purchased from Aladdin and J&K® chemical companies were used without further purification. Purification of reaction products was carried out by flash chromatography using Qing Dao Sea Chemical Reagent silica gel (200–300 mesh). The mixture to afford the pure product as indicated by TLC, the mixture was filtered, and the filtrate was concentrated in vacuo. The resulting crude product was purified by column chromatography by using an EtOAc/petroleum ether gradient mixture to afford the pure product.

1H-NMR (400 MHz, CDCl3): δ = 8.43 (d, J = 7.8 Hz, 1 H), 7.63–7.51 (m, 3 H), 7.47–7.43 (m, 3 H), 7.42–7.27 (m, 6 H), 7.20 (s, J = 7.3 Hz, 1 H), 6.70 (s, 1 H).

13C NMR (101 MHz, CDCl3): δ = 151.6, 149.8, 146.8, 134.0, 132.5, 132.9, 129.5, 128.8, 128.2, 125.7, 124.7, 123.7, 122.6, 100.9.

HRMS (ESI): m/z [M + H]+ calcd for C18H16NO+: 262.1226; found: 262.1222.

(Z)-N,N-Diphenyl-1H-isochromen-1-imine (2b)  
Yield: 32.7 mg (54%); yellow solid.

1H NMR (400 MHz, CDCl3): δ = 8.35 (d, J = 7.9 Hz, 1 H), 7.47–7.51 (m, 1 H), 7.34–7.41 (m, 3 H), 7.24–7.28 (m, 4 H), 7.19–7.20 (m, 1 H), 7.13 (t, J = 7.3 Hz, 1 H), 6.95–6.97 (m, 1 H), 6.51 (s, 1 H).

13C NMR (101 MHz, CDCl3): δ = 149.2, 147.7, 146.4, 136.1, 133.8, 132.5, 128.7, 127.9, 127.6, 126.7, 125.4, 125.2, 123.8, 123.5, 122.7, 100.0.

HRMS (ESI): m/z [M + H]+ calcd for C18H16NO+: 262.1226; found: 262.1222.

(Z)-N-Phenyl-3-(thiophen-2-yl)-1H-isochromen-1-imine (2a)  
Yield: 20.8 mg (35%); black solid.

1H NMR (400 MHz, CDCl3): δ = 7.77 (s, 1 H), 7.65–7.53 (m, 2 H), 7.48–7.40 (m, 2 H), 7.16–7.08 (m, 3 H), 6.99–6.92 (m, 2 H), 6.66–6.61 (m, 1 H), 6.35 (s, 1 H), 5.93 (s, 1 H), 5.39 (d, J = 7.9 Hz, 1 H), 5.20 (s, 1 H), 4.82 (s, 1 H), 4.74 (s, 1 H), 3.87 (s, 1 H), 3.84 (s, 1 H).

13C NMR (101 MHz, CDCl3): δ = 152.0, 149.7, 146.8, 134.5, 133.8, 126.0, 129.0, 128.7, 128.2, 127.4, 125.8, 124.0, 123.5, 115.9, 102.1, 18.7.


N-Phenyl-3-[(Z)-prop-1-en-1-yl]-1H-isochromen-1-imine (2e)  
(Z/E = 3:1)  
Yield: 42.8 mg (82%); brown liquid.

1H NMR (400 MHz, CDCl3): δ = 8.36 (d, J = 7.9 Hz, 1 H), 7.53–7.44 (m, 1 H), 7.41 (d, J = 8.2 Hz, 1 H), 7.38 (d, J = 4.3 Hz, 1 H), 7.34 (d, J = 7.7 Hz, 1 H), 7.31–7.27 (m, 1 H), 7.22–7.11 (m, 2 H), 7.06–7.09 (m, 1 H), 6.17–6.03 (m, 1 H), 5.96 (s, 1 H), 5.88–5.96 (m, 1 H), 1.77–1.79 (m, 3 H).

13C NMR (101 MHz, CDCl3): δ = 150.8, 149.7, 146.7, 134.2, 132.3, 131.9, 129.9, 128.7, 127.9, 127.5, 125.3, 123.6, 122.6, 121.9, 103.0, 18.4.

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(Z)-3-(Cyclohex-1-en-1-yl)-N-phenyl-1H-isochromen-1-imine (2f)
Yield: 45.2 mg (75%); yellow solid.
1H NMR (400 MHz, CDCl3): δ = 8.33 (d, J = 7.9 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 1 H), 7.43–7.30 (m, 3 H), 7.20–7.26 (m, 3 H), 7.10 (t, J = 7.3 Hz, 1 H), 6.62 (s, 1 H), 6.12 (s, 1 H), 2.26–2.02 (m, 4 H), 1.64–1.71 (m, 4 H).
13C NMR (101 MHz, CDCl3): δ = 152.5, 150.0, 146.9, 134.3, 132.2, 128.6, 128.5, 127.6, 127.4, 125.5, 123.7, 123.4, 122.4, 99.4, 25.7, 24.0, 22.3, 21.8.

(2)-7-Methyl-N-phenyl-3-vinyl-1H-isochromen-1-imine (2g)
Yield: 46 mg (88%); yellow solid.
1H NMR (400 MHz, CDCl3): δ = 8.20 (s, 1 H), 7.45–7.29 (m, 3 H), 7.25 (d, J = 7.6 Hz, 2 H), 7.09–7.15 (m, 2 H), 6.14–6.21 (m, 1 H), 6.10 (s, 1 H), 5.56 (d, J = 17.1 Hz, 1 H), 5.20 (d, J = 11.0 Hz, 1 H), 2.45 (s, 3 H).
13C NMR (101 MHz, CDCl3): δ = 148.8, 145.6, 137.6, 132.5, 130.2, 127.7, 126.5, 124.6, 123.0, 122.6, 121.5, 115.7, 104.2, 20.5.

(2)-7-Fluoro-N-phenyl-3-vinyl-1H-isochromen-1-imine (2h)
Yield: 44 mg (83%); yellow solid.
1H NMR (400 MHz, CDCl3): δ = 8.02 (d, J = 9.2 Hz, 1 H), 7.43–7.32 (m, 2 H), 7.28–7.21 (m, 2 H), 7.18–7.25 (m, 2 H), 7.09–7.13 (m, 1 H), 6.13–6.20 (m, 1 H), 6.05 (s, 1 H), 5.58 (d, J = 17.1 Hz, 1 H), 5.21 (d, J = 11.0 Hz, 1 H).
13C NMR (101 MHz, CDCl3): δ = 162.2 (d, J = 248.4 Hz), 149.9 (d, J = 29.9 Hz), 148.5 (s), 146.0 (s), 130.1 (d, J = 2.7 Hz), 128.7 (s), 128.6 (s), 127.6 (d, J = 7.9 Hz), 126.2 (d, J = 8.6 Hz), 124.0 (s), 122.6 (s), 120.3 (d, J = 23.1 Hz), 117.3 (s), 113.7 (d, J = 24.2 Hz), 104.3 (d, J = 1.5 Hz).
HRMS (ESI): m/z [M + H]+ calcd for C18H13FNO+: 266.0976; found: 266.0978.

(2)-7-Chloro-N-phenyl-3-vinyl-1H-isochromen-1-imine (2i)
Yield: 38.5 mg (71%); yellow solid.
1H NMR (400 MHz, CDCl3): δ = 8.31 (d, J = 1.8 Hz, 1 H), 7.47–7.29 (m, 3 H), 7.23 (d, J = 7.4 Hz, 2 H), 7.09–7.13 (m, 2 H), 6.12–6.19 (m, 1 H), 6.02 (s, 1 H), 5.59 (d, J = 17.1 Hz, 1 H), 5.22 (d, J = 11.0 Hz, 1 H).
13C NMR (101 MHz, CDCl3): δ = 150.7, 148.1, 145.9, 134.0, 132.5, 132.1, 128.6, 127.3, 126.9, 125.6, 124.0, 122.6, 117.8, 104.3.

(2)-7-Bromo-N-phenyl-3-vinyl-1H-isochromen-1-imine (2j)
Yield: 33.8 mg (52%); yellow solid.
1H NMR (400 MHz, CDCl3): δ = 8.48 (d, J = 1.4 Hz, 1 H), 7.56–7.58 (m, 1 H), 7.36 (t, J = 7.8 Hz, 2 H), 7.23 (d, J = 7.5 Hz, 2 H), 7.17–7.00 (m, 2 H), 6.13–6.20 (m, 1 H), 6.03 (s, 1 H), 5.60 (d, J = 17.1 Hz, 1 H), 5.24 (d, J = 10.9 Hz, 1 H).
13C NMR (101 MHz, CDCl3): δ = 150.8, 147.9, 145.9, 135.4, 132.5, 130.2, 128.6, 127.0, 125.8, 124.0, 122.5, 121.9, 117.9, 104.4.

(2)-7-(4-Fluorophenyl)-3-vinyl-1H-isochromen-1-imine (2m)
Yield: 44.5 mg (84%); yellow solid.
1H NMR (400 MHz, CDCl3): δ = 8.33 (d, J = 7.9 Hz, 1 H), 7.47–7.51 (m, 1 H), 7.36–7.40 (m, 1 H), 7.32–7.14 (m, 3 H), 7.13–6.98 (m, 2 H), 6.17–6.24 (m, 1 H), 6.09 (s, 1 H), 5.60 (d, J = 17.1 Hz, 1 H), 5.24 (d, J = 11.0 Hz, 1 H).
13C NMR (101 MHz, CDCl3): δ = 159.4 (d, J = 241.8 Hz), 150.4 (s), 142.5 (d, J = 2.9 Hz), 133.6 (s), 132.4 (s), 128.8 (s), 128.3 (s), 127.5 (s), 125.7 (s), 124.1 (t, J = 8.6 Hz), 117.2 (s), 115.4 (s), 115.2 (s), 105.7 (s).
HRMS (ESI): m/z [M + H]+ calcd for C18H13FNO+: 266.0976; found: 266.0980.

(2)-7-(4-Chlorophenyl)-3-vinyl-1H-isochromen-1-imine (2n)
Yield: 44.96 mg (80%); yellow solid.
1H NMR (400 MHz, CDCl3): δ = 8.31 (d, J = 7.9 Hz, 1 H), 7.48–7.52 (m, 1 H), 7.42–7.34 (m, 1 H), 7.35–7.26 (m, 2 H), 7.26–7.12 (m, 3 H), 6.16–6.23 (m, 1 H), 6.10 (s, 1 H), 5.58 (d, J = 17.1 Hz, 1 H), 5.23 (d, J = 11.0 Hz, 1 H).
13C NMR (101 MHz, CDCl3): δ = 150.4, 149.9, 145.1, 133.7, 132.5, 128.7, 128.4, 127.6, 125.7, 124.0, 117.2, 115.4 (s), 115.2 (s), 105.7 (s).
262.1232.

[1H NMR (400 MHz, CDCl₃): δ = 8.30 (d, J = 7.6 Hz, 1 H), 7.51 (d, J = 7.8 Hz, 2 H), 7.45 (t, J = 7.5 Hz, 1 H), 7.33–7.38 (m, 3 H), 7.26 (t, J = 7.1 Hz, 1 H), 7.20 (d, J = 7.7 Hz, 1 H), 6.28–6.34 (m, 1 H), 6.09 (s, 1 H), 5.92 (d, J = 17.1 Hz, 1 H), 5.39 (d, J = 10.9 Hz, 1 H), 4.81 (s, 2 H).


Methyl (Z)-3-Phenyl-2-[(3-vinyl-1H-isochromen-1-ylidene)amino]propanoate (2u)

Yield: 5.46 mg (82%); brown liquid.

[1H NMR (400 MHz, CDCl₃): δ = 8.30 (d, J = 7.7 Hz, 1 H), 7.43–7.47 (m, 1 H), 7.32–7.35 (m, 3 H), 7.30–7.23 (m, 2 H), 7.23–7.13 (m, 2 H), 6.17–6.24 (m, 1 H), 6.03 (s, 1 H), 5.81 (d, J = 17.1 Hz, 1 H), 5.33 (d, J = 11.0 Hz, 1 H), 4.77–4.80 (m, 1 H), 3.67 (s, 3 H), 3.19–3.31 (m, 2 H).


Methyl (Z)-2-[(3-Vinyl-1H-isochromen-1-ylidene)amino]propanoate (2v)

Yield: 65.6 g (85%); brown liquid.

[1H NMR (400 MHz, CDCl₃): δ = 8.29 (d, J = 7.9 Hz, 1 H), 7.51–7.42 (m, 1 H), 7.41–7.29 (m, 5 H), 7.29–7.12 (m, 2 H), 6.19–6.26 (m, 1 H), 6.07 (s, 1 H), 5.78 (d, J = 17.2 Hz, 1 H), 5.21–5.30 (m, 2 H), 5.15 (d, J = 12.4 Hz, 1 H), 4.73 (q, J = 7.0 Hz, 1 H), 1.60 (d, J = 7.0 Hz, 3 H).


(Z)-N-[(7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl]-3-vinyl-1H-isochromen-1-imine (2w)

Yield: 71.2 mg (81%); brown liquid.

[1H NMR (400 MHz, CDCl₃): δ = 8.19 (d, J = 7.6 Hz, 1 H), 7.42 (t, J = 7.0 Hz, 1 H), 7.35–7.21 (m, 2 H), 7.17 (d, J = 7.5 Hz, 1 H), 7.06 (d, J = 7.5 Hz, 1 H), 6.93 (s, 1 H), 6.43–6.24 (m, 1 H), 6.04 (s, 1 H), 5.94 (d, J = 17.1 Hz, 1 H), 5.41 (d, J = 10.8 Hz, 1 H), 3.61 (d, J = 14.6 Hz, 1 H), 3.30 (d, J = 14.6 Hz, 1 H), 2.87 (d, J = 7.0 Hz, 3 H), 2.34 (d, J = 12.1 Hz, 1 H), 2.06–1.85 (m, 2 H), 1.85–1.65 (m, 3 H), 1.52 (d, J = 9.1 Hz, 2 H), 1.41–1.14 (m, 9 H), 1.09–1.04 (m, 4 H).


(Z)-1-(Diphenylmethylene)-2-(3-phenyl-1H-isochromen-1-ylidene)hydrizine (2x)

Yield: 40.8 mg (51%); brown solid.
Yield: 24.8 mg (66%); brown solid.

7-Fluoro-3-vinylisoquinolin-1-amine (4b)

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Supporting Information

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References


N. A. B.; Bittner, D. M.; McFarlane, W.; Wills, C.; Probert, M. R. 


(11) CCDC 1941980 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.