Copper-catalyzed oxidative cross-dehydrogenative coupling of 2H-chromenes and terminal alkynes

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<tr>
<th>Journal:</th>
<th>Organic &amp; Biomolecular Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>OB-ART-04-2018-000949.R1</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Paper</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>03-Jun-2018</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
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Copper-catalyzed oxidative cross-dehydrogenative coupling of 2H-chromenes and terminal alkynes†

Fei Yang,a,b Yangshan Li,a Paul E. Florencig,ab Xiaoyan Li,aa and Lei Li*a

An efficient copper-catalyzed cross-dehydrogenative coupling of 2H-chromenes and terminal alkynes mediated by DDQ has been established. Protic additive EtOH proved to be crucial to harmonizing the oxidation with subsequent alkynylation step by retaining the oxidation state of oxocarbenium ion in the form of acetel. The CDC reaction exhibits good substrate scope, with a range of terminal aryl- and alkylalkynes well tolerated. The copper-catalyzed alkyynylation of 2H-chromene acetals with terminal alkynes were also explored.

Introduction

α-Substituted 2H-chromenes and their analogs represent common structural motifs in numerous biologically active natural products and synthetic pharmaceuticals exhibiting antipsychotic, antibacterial, antifungal, antiviral, anticancer, antioxidative, antidepressive, antihypertensive, and antiabetic activities. Given the significance of this privileged motif in modern pharmacology, developing an efficient, economic, and modular method to its synthesis is of paramount importance. Nucleophilic substitution of 2H-chromene acetals has been recognized as one of the most versatile protocols to access the substructures bearing diverse α-substituent patterns. Elegant methods have been established to install diversely hybridized carbon-centered moieties into the α-position of the skeleton. For examples, Schaus disclosed a chiral Bronsted acid-catalyzed enantioselective vinylation and arylation of 2H-chromene acetals with corresponding boronate esters with excellent enantiocontrol. Moreover, the Doyle group developed a nickel-catalyzed coupling of chromene acetals with aryl boronic acids in high efficiency. Watson reported the catalytic enantioselective alkyynylation of 2H-chromene acetals with a variety of terminal alkynes in the presence of a combination of BF3·OEt2 and dicyclohexyl methyl amine. Rueping and co-workers reported an asymmetrical alkyynylation of 2H-chromene acetals with aldehydes by adopting a synergistic catalytic strategy.

Albeit great innovations, at least one of the two coupling components requires prefunctionalization. The direct cross-dehydrogenative coupling (CDC) of 2H-chromenes with readily available C–H components represents an ideal synthetic strategy with a minimal amount of intermediary refunctionalizations and with high atom economy. In this context, we have reported CDC reactions of 2H-chromenes with 1,3-dicarbonyl compounds and electron-rich arenes, providing respective alkylation and arylation compounds. However, the corresponding CDC of 2H-chromenes with terminal alkynes has never been established to date, which might be ascribed to their relatively weak nucleophilicity compared to 1,3-dicarbonyl compounds and electron-rich arenes. In addition, alkyn moiectes are pervasive structural elements in chemistry, biology, material science, and medicine, and serve as versatile handles for a variety of functional groups. Particularly, replacing the complicated α-substitutions of anticancer alkaloids with simple alkyn moieties has recently been demonstrated as a practical strategy to maintain the intrinsic biological activity while simplifying the whole synthesis. Therefore, a practical and efficient CDC of 2H-chromenes with terminal alkynes to rapidly access a multitude of α-substituted chromene analogs remains highly desired.

Results and discussion

Initially, the CDC of 2H-chromene 1a and phenylacetylene 2a using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as the oxidant was selected as the model reaction for optimization (Table 1). No expected alkynylation product 3a was observed when CuBr was employed as the catalyst (entry 1, Table 1). Since DDQ has been demonstrated to effect the oxidation of 1a, such observation might be ascribed to the low stability of oxidized oxocarbenium intermediate towards the subsequent capture by 2a. We envisioned that a protic additive might be beneficial to harmonize the oxidation with subsequent alkynylation. When one equiv of EtOH was introduced, desired 3a was isolated in 8% yield (entry 2, Table 1). The reaction at 80 °C afforded an improved yield of 21% (entry 3, Table 1). Next, an extensive investigation of different copper catalysts revealed Cu(CN)4PF6 as the ideal choice, furnishing 3a in 60% yield (entries 4-10, Table 1). Other protic additives like MeOH and iPrOH did not provide better results (entries 10-12, Table 1). The reaction proved to be highly dependent on the solvent choice; performing the oxidation in CH2Cl2 and subsequent coupling in toluene gave...
the expected 3a in 80% yield (entry 13, Table 1). The use of K2CO3 as the additive was found to be beneficial for improving the yield to 82% (entry 14, Table 1). Inferior results were obtained when other common oxidants for CDC reactions including PhI(OAc)2, Na2S2O8, MnO2, and tert-butyl hydroperoxide (TBHP) were used (entry 15, Table 1).

Table 1. Reaction condition optimization.*

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<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Yield (%)</th>
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*General conditions: 1a (0.1 mmol), DDQ (0.11 mmol), and additive (0.11 mmol) in CICH2CH2Cl (1.0 mL) at rt for 1 h, followed by 2a (0.15 mmol), and catalyst (10 mol%) at rt for 5 h. 'Isolated yield.' Performing the oxidation in CICH2CH2Cl at rt, and coupling in at 80 °C. 'Performing the oxidation in CH2Cl2 (0.5 mL) at rt, followed by alkynylation in toluene (1.2 mL) at 80 °C.' Reaction with 0.3 equiv of K2CO3. 'PhI(OAc)2, Na2S2O8, MnO2, or TBHP as the oxidant.

With the optimized reaction condition in hand, we investigated the scope of the CDC of 2H-chromones with terminal alkynes (Scheme 1). The reaction proved to be fairly general for a variety of electronically varied aryl acetylenes with different substituent patterns (3a-3i). Electron-donating moieties (3b-3d) together with electron-withdrawing halides (3e-3h) and trifluoromethyl (3i) ones were well tolerated with up to 85% yield. 2-Naphthyl acetylene (3j) and heteroaryl acetylenes (3k and 3l) were viable coupling components. Besides ary lacetylenes, alkyl acetylene was also found to be compatible with the CDC reaction, as demonstrated by the generation of 3m in 63% yield. The CDC of electronically varied 2H-chromones with different substituent patterns with and diverse aryl acetylenes proceeded smoothly, providing 3n-3s in high efficiency. The mild CDC reaction exhibits good functional group compatibility for further manipulations.

During the standard CDC reaction of 1a with 2a, a considerable amount of an intermediate was observed by TLC analysis, which was identified as EtOH adduct acetal 4 (Scheme 2). Accordingly, a control experiment was performed to explore the role of EtOH by subjecting 4 to the standard CDC conditions (Scheme 2). Comparable yields to those of CDC processes were obtained, suggesting that acetal 4 might be an intermediate for the CDC process.

Scheme 1. The CDC reaction scope. *Reaction in 1.0 g scale.

Scheme 2. Alkyynylation of 2H-chromene acetals.

The DDQ-mediated oxidation of 2H-chromones was significantly suppressed by adding stoichiometric amount of radical inhibitor 2,6-di-tert-butyl-4-methylphenol (BHT) or TEMPO, thus indicating that a radical intermediate might be involved. Based on these preliminary studies, a plausible mechanism was proposed (Scheme 3). 2H-chromene 1a might...
undergo a single electron transfer (SET) to DDQ giving radical cation 5, which then proceeds through a hydrogen atom abstraction or proton abstraction followed by a SET to generate α,β-unsaturated oxocarbenium intermediate 6. A stoichiometric protic additive EtOH rapidly capture 6 to give 2H-chromene acetal 4 for subsequent alkylation.

Scheme 3. A proposed mechanism.

Conclusions

In conclusion, an efficient copper-catalyzed CDC of 2H-chromenes and terminal alkynes using DDQ as the oxidant is described. Protic additive EtOH proved to be crucial to harmonizing the oxidation with subsequent alkylation step by retaining the oxidation state of oxocarbenium ion in the form of acetal. The copper-catalyzed alkylation of 2H-chromene acetals with terminal alkynes were also explored. Ongoing studies focus on the developing the catalytic asymmetric variant of on the discovery of biologically important small molecules.

Experimental

Proton (1H NMR) and carbon (13C NMR) nuclear magnetic resonance spectra were recorded at 500 MHz and 125 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for 1H NMR: CDCl3 = 7.27 ppm, for 13C NMR: CDCl3 = 77.23 ppm. Analytical TLC was performed on precoated silica gel GF254 plates. HRMS were carried out using an Orbitrap analyzer.

General procedure for the oxidative C–H alkylation of 2H-chromenes (Scheme 1)

To a solution of 2H-chromene 1a (0.1 mmol, 1.0 eq) in CH2Cl2 (0.5 mL) was added EtOH (0.14 mmol, 1.4 eq) and DDQ (0.12 mmol, 1.2 eq) successively at rt. The mixture was stirred at that temperature under N2 atmosphere until all the 1a disappeared monitored by TLC. Then toluene (1.2 mL) was added and volatiles were removed under reduced pressure. After that, Cu(CN)4PF6 (0.01 mmol, 10 mol%), K2CO3 (0.03 mmol, 0.3 eq), and terminal alkyne (0.15 mmol, 1.5 eq) were added, and the mixture was stirred at 80 °C for 5 h. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel using EtOAc/petroleum ether (5 : 95) as an eluent to afford 3a as a light yellow oil (19.0 mg, 82% yield). 1H NMR (500 MHz, CDCl3) δ 7.46–7.40 (m, 2H), 7.33–7.27 (m, 3H), 7.17 (t, J = 7.9, 1.2 Hz, 1H), 7.07–7.02 (m, 1H), 6.97–6.88 (m, 2H), 6.53 (d, J = 9.4 Hz, 1H), 5.85 (dd, J = 9.5, 4.0 Hz, 1H), 5.83–5.79 (m, 1H); 13C NMR (126 MHz, CDCl3) δ 152.6, 152.1, 129.7, 128.8, 128.4, 126.9, 124.3, 122.8, 122.2, 122.0, 121.6, 116.6, 86.2, 85.9, 65.2; HRMS (EI) m/z [M + H]+ calculated for C18H15O2: 263.1067, found 263.1059.

2-(p-Tolylethynyl)-2H-chromene (3b)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford 3b as a yellow oil (19.2 mg, 78% yield). 1H NMR (500 MHz, CDCl3) δ 7.36–7.30 (m, 2H), 7.20–7.15 (m, 1H), 7.10 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 7.2 Hz, 1H), 6.93 (t, J = 7.4 Hz, 2H), 6.52 (d, J = 9.5 Hz, 1H), 5.86 (dd, J = 9.5, 3.9 Hz, 1H), 5.83–5.79 (m, 1H), 2.34 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 152.6, 139.0, 132.0, 129.0, 129.6, 129.1, 126.9, 124.7, 122.4, 121.9, 121.6, 119.2, 116.6, 86.0, 85.5, 65.3, 21.6; HRMS (EI) m/z [M + H]+ calculated for C23H23O: 327.1597, found 327.1596.

2-(m-Tolylethynyl)-2H-chromene (3e)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford 3e as a light yellow oil (18.6 mg, 76% yield). 1H NMR (500 MHz, CDCl3) δ 7.26–7.21 (m, 2H), 7.20–7.14 (m, 2H), 7.12 (d, J = 7.7 Hz, 1H), 7.04 (dd, J = 7.4, 1.6 Hz, 1H), 6.95–6.89 (m, 2H), 6.52 (dd, J = 9.5, 0.8 Hz, 1H), 5.85 (dd, J = 9.5, 4.0 Hz, 1H), 5.80 (dd, J = 4.0, 1.5 Hz, 1H), 2.30 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 152.6, 138.0, 132.6, 129.7, 129.6, 129.1, 128.2, 126.9, 124.7, 122.3, 121.2, 121.9, 121.6, 116.6, 86.0, 85.8, 65.2, 21.3; HRMS (EI) m/z [M + H]+ calculated for C18H15O: 247.1117, found 247.1110.

2-(4-Methoxyphenyl)ethynyl)-2H-chromene (3d)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford 3d as a light yellow oil (16.2 mg, 62% yield). 1H NMR (500 MHz, CDCl3) δ 7.40–7.33 (m, 2H), 7.15 (td, J = 7.8, 1.6 Hz, 1H), 7.03 (dd, J = 7.4, 1.5 Hz, 1H), 6.95–6.87 (m, 2H), 6.84–6.77 (m, 2H), 6.51 (d, J = 9.5 Hz, 1H), 5.84 (dd, J = 9.5, 3.9 Hz, 1H), 5.79 (dd, J = 3.9, 1.5 Hz, 1H), 3.79 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 160.0, 152.7, 133.6, 129.6, 126.9, 124.7, 122.5, 121.9, 121.6, 116.6, 86.0, 85.8, 95.9, 54.4; HRMS (EI) m/z [M + H]+ calculated for C19H17O2: 266.1007, found 266.1007.

2-(4-Bromophenyl)ethynyl)-2H-chromene (3e)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford 3e as a light yellow oil (25.6 mg, 83% yield). 1H NMR (500 MHz, CDCl3) δ 7.42 (d, J = 8.3 Hz, 2H), 7.31–7.27 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 6.97–6.86 (m, 2H), 6.52 (d, J = 9.5 Hz, 1H), 5.88–5.76 (m, 2H); 13C NMR (126 MHz, CDCl3) δ 152.5, 133.5, 132.1, 131.7, 129.7, 128.4, 127.0, 124.9, 123.2, 122.0, 121.4, 116.6, 85.9, 84.9, 65.4, 55.4; HRMS (EI) m/z [M + H]+ calculated for C19H13BrO2: 326.0467, found 326.0467.
It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford 3f as a light yellow oil (22.2 mg, 84% yield). 1H NMR (500 MHz, CDCl3) δ 7.36–7.31 (m, 2H), 7.27–7.23 (m, 2H), 7.16 (td, J = 7.8, 1.6 Hz, 1H), 7.04 (dd, J = 7.4, 1.5 Hz, 1H), 6.95–6.88 (m, 2H), 6.52 (d, J = 9.4 Hz, 1H), 5.83 (dd, J = 9.4, 4.0 Hz, 1H), 5.79 (dd, J = 4.0, 1.3 Hz, 1H); 13C NMR (126 MHz, CDCl3) δ 152.5, 134.9, 133.3, 132.7, 128.7, 127.0, 124.9, 122.0, 121.9, 121.5, 120.8, 116.6, 87.2, 84.7, 65.1; HRMS (EI) m/z [M + H]+ calculated for C17H12FO: 251.0870, found 251.0867.

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5 : 95) as an eluent to afford 3g as a light yellow oil (20.7 mg, 83% yield). 1H NMR (500 MHz, CDCl3) δ 7.43–7.38 (m, 2H), 7.19 (dd, J = 7.8, 1.6 Hz, 1H), 7.05 (dd, J = 7.4, 1.6 Hz, 1H), 7.01–6.96 (m, 2H), 6.95–6.89 (m, 2H), 6.53 (d, J = 9.5 Hz, 1H), 5.84 (dd, J = 9.5, 4.0 Hz, 1H), 5.80 (dd, J = 4.0, 1.3 Hz, 1H); 13C NMR (126 MHz, CDCl3) δ 163.8, 161.9, 152.5, 134.0, 129.7, 127.0, 124.8, 122.0, 121.5, 118.4, 116.6, 115.7, 85.9, 84.8, 65.1; HRMS (EI) m/z [M + H]+ calculated for C17H12BrO: 311.0061, found 311.0066.
6-Methyl-2-(p-tolylenyl)-2H-chromene (3o)

It was prepared following the general procedure and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (5:95) as an eluent to afford 3o as a light yellow oil (21.5 mg, 83% yield). 1H NMR (500 MHz, CDCl3) δ 7.38–7.34 (m, 4H), 7.27–7.24 (m, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 9.6 Hz, 1H), 5.90 (dd, J = 9.6, 4.1 Hz, 1H), 5.80 (dd, J = 4.1, 1.5 Hz, 1H); 13C NMR (126 MHz, CDCl3) δ 151.7, 132.3, 132.2, 129.5, 128.0, 128.5, 123.8, 123.5, 123.2, 118.5, 114.1, 86.4, 85.6, 65.4; HRMS (EI) m/z [M + H]+ calculated for C23H20O: 311.0066, found 311.0075.

General procedure for the alkylation of 2H-chromenes (Scheme 2)

To a solution of 2H-chromene 4 (0.1 mmol, 1.0 eq) in toluene (1.0 mL) was added Cu(CN)2PF6 (0.01 mmol, 10 mol%) and terminal alkylne (0.15 mmol, 1.5 eq). The mixture was stirred at 80 °C for 3 h before the volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel using EtOAc/petroleum ether (5:95) as an eluent to give the desired product.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the National Science Foundation of China (21722204 and 21472112), the National Institutes of Health (R01GM103886), and the Fok Ying Tung Education Foundation (151035).

Notes and references


A practical cross-dehydrogenative coupling of 2H-chromenes with terminal alkynes is described.