



Palladium-catalyzed [3+2+1] cyclocarbonylative coupling of 1,3-cyclohexanediones, alkynes, and carbon monoxide: an atom-economic route to chromene-2,5-dione derivatives

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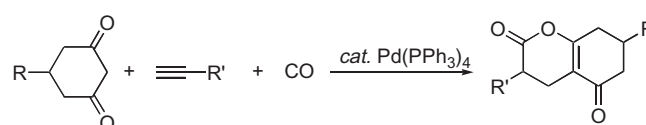
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ABSTRACT

3,4,7,8-Tetrahydro-2*H*-chromene-2,5(6*H*)-dione derivatives were efficiently synthesized with excellent selectivity via a [3+2+1] cyclocarbonylative coupling of 1,3-cyclohexanediones, terminal alkynes, and CO catalyzed by Pd(PPh₃)₄.

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One-pot multi-component reactions are of considerable current interest, since they can rapidly construct functionalized molecules of great complexity.¹ In the last two decades, remarkable progress has been achieved in transition metal-catalyzed cycloaddition reactions using alkyne as one of components to synthesize various functionalized cyclic compounds, with the advantages of atom-economic processes, easily available starting materials, and controllable regioselectivity of cycloadducts.² On the other hand, cyclic β-diketones, owing to their tautomeric property have been also well applied in the synthesis of fused cyclic compounds.³ In our development of atom-economic reactions for the synthesis of cyclic carbonyl compounds via cyclocarbonylative coupling of alkynes, we have established the catalytic systems for highly selective synthesis of furan-2(5*H*)-ones, *p*-benzoquinones, and 2-cyclopenten-1-ones.⁴ In continuation of our research on the cyclocarbonylation of alkynes, we designed, in the present work, a three-component [3+2+1] cyclocarbonylative coupling of 1,3-cyclohexanediones, alkynes, and CO in the presence of Pd(PPh₃)₄ to develop an atom-economic process for the synthesis of 3,4,7,8-tetrahydro-2*H*-chromene-2,5(6*H*)-dione derivatives. These derivatives are considered to be versatile and important bicyclic intermediates in the synthesis of biologically active and pharmaceutical O-heterocyclic molecules (Scheme 1).



Scheme 1. Atom-economic route for synthesis of chromene-2,5-diones.

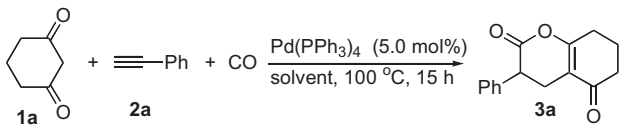
The reactions of 1,3-cyclohexanedione (**1a**), phenyl acetylene, (**2a**) and CO in the presence of 5 mol % of Pd(PPh₃)₄ at 100 °C under different reaction conditions were examined to optimize the catalytic system and the results are concluded in Table 1. We found that when an excess amount of **2a** was used (3.0 equiv),⁵ the cyclocarbonylative coupling reactions under different CO pressures (1.0, 3.0, and 5.0 MPa) and a variety of solvents such as THF, toluene, DMSO, dioxane, DMF, CH₃CN, and Cl₂CHCHCl₂ (TCE) furnished the desired cycloadduct **3a** in fair to moderate yields only (entries 1–10), and the best yield of **3a** in 56% was achieved in THF under a CO pressure of 5.0 MPa (initial pressure at room temperature) (entry 4). Therefore, under the conditions of entry 4, the reaction was conducted again using 1.5 equiv of **1a** and fortunately it was found that **3a** was formed in 82% GC yield (entry 12). In addition, the use of Pd(II) complexes, such as PdCl₂(PPh₃)₂, Pd(OAc)₂, and PdCl₂ showed no catalytic activity for the present cyclocarbonylative coupling reaction.

It should be also noted that in all the reactions, **3a** was formed as an exclusive three-component cyclocoupling product, no other

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Table 1

Palladium(0)-catalyzed cyclocarbonylative coupling of 1,3-cyclohexanedione (**1a**), phenylacetylene (**2a**), and CO under different conditions^a



Entry	1a:2a	CO (MPa) ^b	Solvent	GC yield (%) ^c
1	1:3	1.0	THF	20
2	1:3	3.0	THF	40
3 ^d	1:3	5.0	THF	33
4	1:3	5.0	THF	56
5	1:3	5.0	Toluene	31
6	1:3	5.0	DMSO	36
7	1:3	5.0	Dioxane	45
8	1:3	5.0	DMF	36
9	1:3	5.0	TCE	11
10	1:3	5.0	CH ₃ CN	10
11 ^e	1.5:1	5.0	THF	82 (77) ^f

^a Unless otherwise noted, reactions were carried out at 100 °C for 15 h by using 1.0 mmol of **1a** and 0.05 mmol of Pd(PPh₃)₄ in 1.0 mL of solvent in a 15 mL autoclave.

^b Initial pressure at ambient temperature.

^c GC yield based on the amount of **1a** used.

^d 11 h.

^e 1.5 mmol of **1a** and 1.0 mmol of **2a** were used.

^f GC yield based on the amount of **2a** used. Number in parenthesis is isolated yield.

regioisomer with the same molecular weight could be detected by GC and GC–MS of the reaction mixture. The regioselectivity of the phenyl group bonded to α -position of carbonyl group (ester) is supported by its ¹H NMR spectroscopic data, in which only a single proton is observed at 3.80 ppm (proton of alkyl group appears at the lowest field) assigned to the α -proton of ester, and which was finally confirmed by X-ray crystallography (Fig. 1).⁶

Utilizing optimized conditions, the [3+2+1] cyclocarbonylative coupling process was then applied to the other alkynes. As summarized in Table 2, the reaction of aromatic alkynes bearing either an electron-donating group of methyl (**2b**) or an electron-withdrawing group of chloro (**2c**) underwent the reaction smoothly to give the corresponding cycloadducts **3b** and **3c** in 85% and 74% isolated yields, respectively (Table 2, entries 1–2). Additionally, the substituted 1,3-cyclohexanediones such as 5,5-dimethyl-1,3-cyclohexanedione (**1b**) and 5-phenyl-1,3-cyclohexanedione (**1c**) were also suitable cyclocoupling partners under the same reaction conditions to give the expected products **3d–g** in good to high yields (Table 2, entries 3–6).

Although the use of 1-octyne in different solvents resulted in the formation of a complicated mixture containing a low yield of the expected bicyclic compound, it was found that the reactions of **1a–c** with 2-methyl-1-buten-3-yne (**2d**) under similar condi-

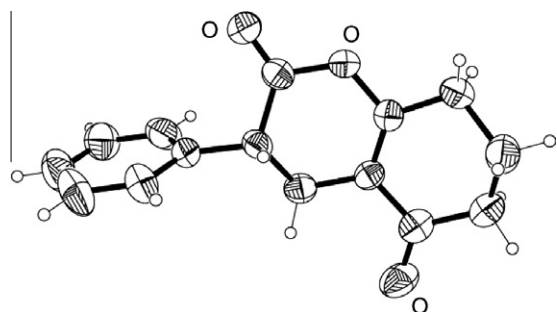
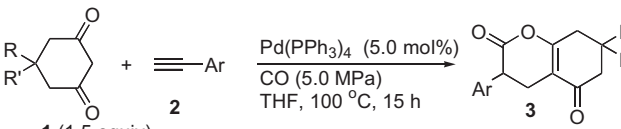


Figure 1. Molecular structure of **3a**.

Table 2

Palladium(0)-catalyzed cyclocarbonylative coupling of 1,3-cyclohexanediones, alkynes, and carbon monoxide^a

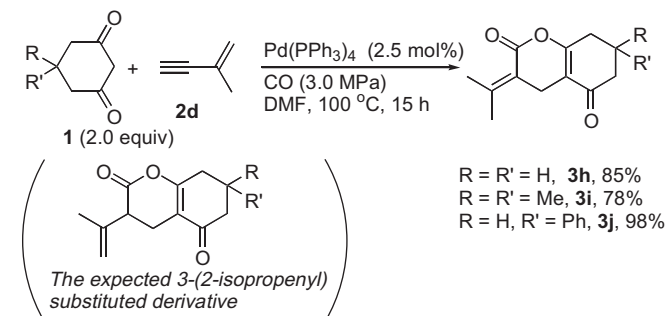


Entry	R	R'	Ar	Cycloadduct 3	Yield (%) ^b
1	H	H	<i>p</i> -MeC ₆ H ₄ 2b	3b	85
2	H	H	<i>p</i> -ClC ₆ H ₄ 2c	3c	74
3	Me	Me	Ph 2a	3d	70
4	Me	Me	<i>p</i> -MeC ₆ H ₄ 2b	3e	69
5	Me	Me	<i>p</i> -ClC ₆ H ₄ 2c	3f	84
6	H	Ph	Ph 2a	3g	96

^a Reactions were carried out at 100 °C for 15 h by using 1.5 mmol of **1**, 1.0 mmol of **2** and 0.05 mmol of Pd(PPh₃)₄ in THF (1.0 mL) mL in a 15 mL autoclave. Isolated yield based on **2** used.

^b On the basis of ¹³C NMR spectrum of **3g**, the diastereomeric ratio is ca. 1:1.

tions using DMF as the solvent to replace THF afforded the cyclocarbonylative coupling product **3h–j** in good to high isolated yields (Scheme 2). The structure of **3j** with isopropylidene group at 3 position was unambiguously confirmed by X-ray crystallography (Fig. 2),⁶ and indicated that the double bond shift isomerization of isopropenyl group to isopropylidene occurred.



Scheme 2. Carbonylative cyclocoupling of 1,3-cyclohexanediones, 2-methyl-1-buten-3-yne, and carbon monoxide.

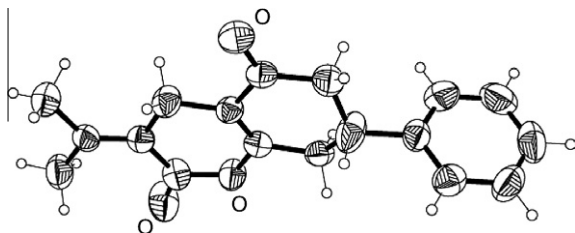


Figure 2. Molecular structure of **3j**.

The route for the formation of chromene-2,5-dione derivatives is proposed to involve the oxidative addition of O–H bond of enol of **1** to Pd(0), insertion of CO, and alkyne to Pd–O bond, as well as intramolecular cyclization.

In conclusion, we have developed a [3+2+1] cyclocarbonylative coupling of 1,3-cyclohexanediones, terminal alkynes, and CO in the presence of Pd(PPh₃)₄ to provide a straightforward and atom-economic process for the synthesis of 3,4,7,8-tetrahydro-2*H*-chromene-2,5(6*H*)-dione derivatives in good to high yields. The present work extends the application of alkynes and 1,3-cyclohexanediones in the synthesis of bicyclic compounds.

A typical experimental procedure for carbonylative cyclocoupling of 1,3-cyclohexanedione (**1a**), phenylacetylene (**2a**), and CO to afford 3-phenyl-3,4,7,8-tetrahydro-2*H*-chromene-2,5(6*H*)-dione (**3a**) (Table 1, entry 11): 1,3-cyclohexanedione (168.0 mg, 1.5 mmol), phenylacetylene (102.0 mg, 1.0 mmol), Pd(PPh₃)₄ (57.8 mg, 0.05 mmol), and THF (1 mL) were placed in a 15 mL autoclave under a flow of nitrogen, and then carbon monoxide was introduced at an initial pressure of 5.0 MPa at room temperature. The autoclave was heated in an oil bath at 100 °C with stirring for 15 h. After release of CO at room temperature, the crude reaction mixture was diluted with CH₂Cl₂ (4.0 mL) and then *n*-docosane (93.0 mg, 0.3 mmol) was added as an internal standard for GC analysis. After GC and GC–MS analyses of the reaction mixture, volatiles were removed under a reduced pressure, and the residue was subjected to silica gel column chromatography [eluting with petroleum ether and then with a mixture of petroleum ether and ethyl acetate (8:1–4:1)]. **3a** was obtained in 186.3 mg (0.77 mmol, 77%) as a white solid. The GC analysis of the reaction mixture disclosed the formation of **3a** in 82% GC yield. Data for **3a**: White solid, mp 179–180 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.31–7.14 (m, 5H), 3.80 (dd, 1H, *J* = 10.3, 7.6 Hz), 2.95 (dd, 1H, *J* = 16.8, 5.8 Hz), 2.73 (dd, 1H, *J* = 11.3, 8.0 Hz), 2.50 (m, 2H), 2.39 (t, 2H, *J* = 6.3 Hz),

2.10–1.95 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 197.0, 167.9, 167.2, 135.8, 129.0, 128.1, 127.9, 114.4, 44.8, 36.5, 27.1, 24.2, 20.7. GC–MS *m/z* (% rel inten.): 242 (M⁺, 9), 214 (100), 185(16), 118 (65), 115 (42), 90 (44), 77(12). IR (KBr): 1771, 1655 cm⁻¹ (ν_{CO}). Anal. Calcd for C₁₅H₁₄O₃: C, 74.38; H, 5.78. Found: C, 74.44; H, 5.87.

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Supplementary data

Supplementary data (General method, characterization data, charts of ¹H, ¹³C NMR for all the products and the X-ray structural details for **3a** and **3j** are concluded) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.132.

References and notes

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- Considering the possible dimerization and trimerization of terminal alkynes in the presence of Pd(PPh₃)₄, the reactions were first carried out using an excess amount of **2a**.
- Single crystals of **3a** and **3j** for X-ray diffraction analysis were obtained by recrystallization from a mixture of *n*-hexane and CH₂Cl₂. CCDC785612 (**3a**), and CCDC785613 (**3j**) contain Supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk.