Pergamon

Tetrahedron Letters 39 (1998) 5061–5064

TETRAHEDRON LETTERS

Selective Synthesis of 3-Isochromanones by Rhodium-Catalyzed Carbonylation of 2-Alkynylbenzylalcohols under Water-Gas Shift Reaction Conditions

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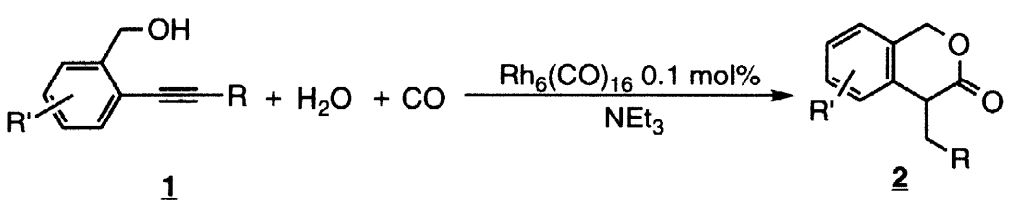
Received 2 April 1998; revised 6 May 1998; accepted 8 May 1998

Abstract: Rhodium-catalyzed cyclic carbonylation of 2-ethynylbenzylalcohols **1** under water-gas shift reaction conditions gives selectively 3-isochromanones **2** which are derived from **1** and one molecule each of hydrogen and carbon monoxide with incorporation of the hydroxymethyl group adjacent to the ethynyl group.

Heterocycles are frequently involved as a principal structure in medicines and pesticides. The cyclic carbonylation of alkenes and alkynes provides an important method for the synthesis of heterocyclic compounds.[1] We have previously showed[2] that the rhodium-catalyzed carbonylation of alkynes under water-gas shift reaction (WGSR) conditions proceeds with a different type of reaction from that under synthesis gas (hydrogen and carbon monoxide), and affords selectively cyclic esters, i. e., lactones, although WGSR is usually used in the industrial production of molecular hydrogen from water with carbon monoxide as well as in the hydrogenation and hydroformylation of alkenes.[3] We have also paid attention to the carbonylation of alkynes having functional groups adjacent to the ethynyl groups and found a novel cyclic carbonylation in which the functional groups such as amino[4], formyl[5] and ester[6] groups participate in constructing heterocyclic products. Recently, we found that the carbonylation of 2-alkynylphenols gave two kinds of products, 3-substituted benzofuranone and coumarin in a total yield of 90% in a ratio of about 1 : 1, but we were unable to improve the product selectivity toward coumarin.[7] However, consideration of the reaction mechanism suggested to us that the hydroxy group of 2-alkynylbenzylalcohol may participate more effectively in the cyclic carbonylation of alkynes. Here, we report that the $Rh_6(CO)_{16}$-catalyzed cyclic carbonylation of 2-alkynylbenzylalcohols under WGSR conditions gives bioactive isochromanone derivatives in high yield with high selectivity (Scheme 1).



1 **2**

Scheme 1

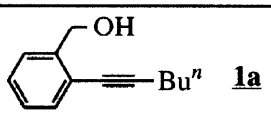
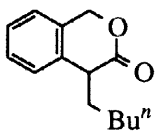
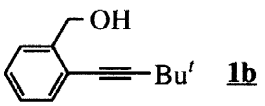
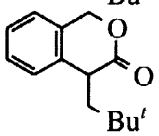
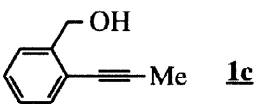
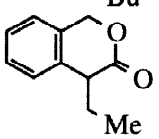
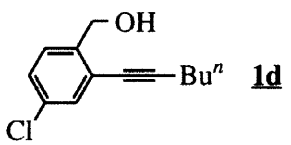
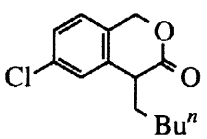
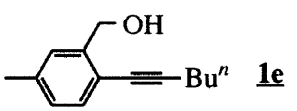
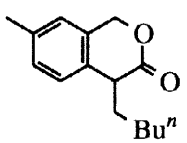
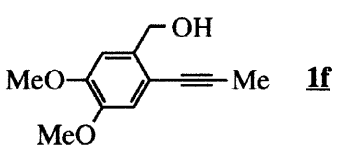
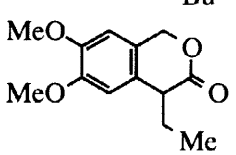
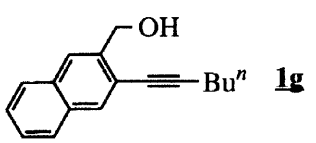
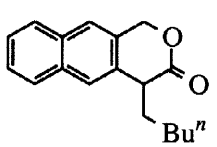
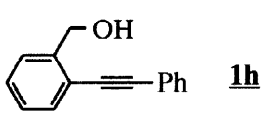
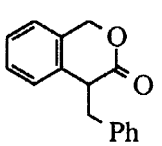
Thus, a mixture of 2-(1-hexynyl)benzyl alcohol **1a** (1 mmol), triethylamine (15 mmol) and H_2O (4 mmol) in 1,4-dioxane (60 ml) was stirred at 175 °C for 5 h under 100 atm of carbon monoxide. After usual work-up, isolation by column chromatography on silica using ethyl acetate and hexane gave 4-pentyl-3-isochromanone **2a**[8] in high yield (91% HPLC yield, and 72% isolated yield). As a by-product, indanone **3a**[9] was detected in 8%

PII: S0040-4039(98)00953-8

HPLC yield in which the hydroxy group remained intact. When the reaction of **1** was carried out under synthesis gas ($CO + H_2$), isochromanone derivatives were not formed.

Product **2a** was identified by ^{1}H-NMR, IR, and mass spectra and elemental analyses. The mass spectrum of **2a** showed an m/z of 218 (M^+) corresponding to the sum of the mass number of 188 (starting substrate **1a**) and 30 ($CO + H_2$). In the IR spectrum, a characteristic absorption appeared at 1747 cm^{-1} due to the carbonyl group of a cyclic ester, and the ^{1}H-NMR spectrum is consistent with the isochromanone structure of **2a**.

Table 1 Cyclic carbonylation of **1**

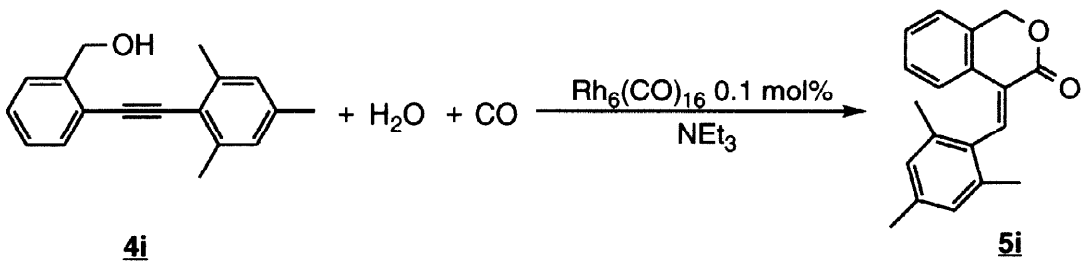
Entry	Substrate		Product		Yield(%)[a]
1		**1a**		**2a**	90 (72)
2		**1b**		**2b**	89 (75)
3		**1c**		**2c**	85 (68)
4		**1d**		**2d**	78 (52)
5		**1e**		**2e**	85 (70)
6		**1f**		**2f**	81 (62)
7		**1g**		**2g**	91 (77)
8		**1h**		**2h**	52 (33)

Reaction conditions: substrate, 1.0 mmol; $Rh_6(CO)_{16}$, 0.001 mmol; 1,4-dioxane, 15 ml; triethylamine, 15.0 mmol; water, 4.0 mmol; reaction temperature, 175 °C; CO pressure, 100 atm; reaction time, 5 h.

a) Yields are determined by HPLC; parentheses indicate isolated yields.

Addition of triethylamine to the reaction system strongly affects the product selectivity. In the absence of triethylamine, the reaction did not occur and the benzylalcohol was recovered, indicating that triethylamine is requisite for initiating the present reaction. Addition of triethylamine of more than about ten equivalents to the substrate resulted in the best yield of **2a**, and decreasing the amount of additive triethylamine increased the yield of by-product **3a**, although in the carbonylation of phenol derivatives the product selectivity did not depend on the amount of additive triethylamine.[7]

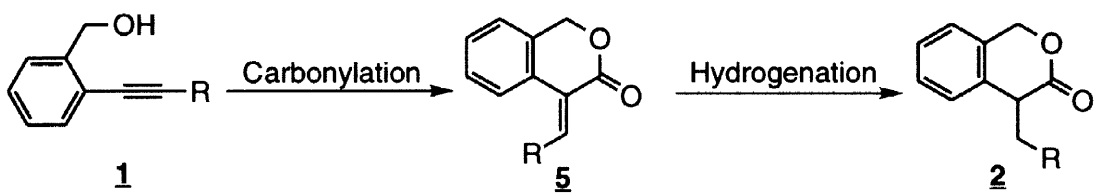
The carbonylation of several kinds of 2-alkynylbenzylalcohol derivatives **1** with different substituent R on the ethynyl group and R' on the aromatic ring were carried out and the results obtained are summarized in Table 1. Most of the reactions proceeded smoothly to give product **2** in excellent yield (Table 1, entries 1-7). The reaction of 2-(phenylethynyl)benzylalcohol **1h** (R = phenyl group) gave the corresponding 3-isochromanone in a rather low yield of 52% (entry 8) along with 1-indanone derivatives as by-products, which are produced by a carbonylation accompanying C-H activation on the phenyl group of **1h**.



4i **5i**

Scheme 2

To suppress the formation of indanones, we carried out the carbonylation of **4i** having no ortho-hydrogen on the phenyl group and obtained **5i**[10] in 71% yield having an exo-methylene group, which originates from the triple bond in **4i** (Scheme 2), indicating that the cyclic carbonylation reaction may proceed via an intermediate (**5**), followed by hydrogenation to **2** (Scheme 3). Hydrogenation of **5i** may be inhibited by steric hindrance of the mesityl group.



1 **5** **2**

Scheme 3

The present cyclic carbonylation may provide a practical method for the synthesis of bioactive 3-isochromanone derivatives because the starting materials, benzylalcohols, are easily prepared from a Pd-Cu catalyzed C-C coupling reaction between alkynes and halobenzylalcohols.[11]

References and Notes

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4. K. Hirao, N. Morii, T. Joh, and S. Takahashi, *Tetrahedron Lett.*, **1995**, 36, 6243.
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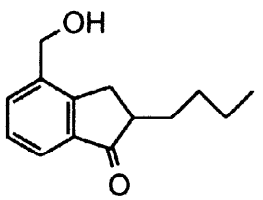
6. T. Sugioka, E. Yoneda, S.-W. Zhang, and S. Takahashi, *Tetrahedron, Lett.*, **1997**, 38, 3005.
7. E. Yoneda, T. Sugioka, K. Hirao, S.-W. Zhang and S. Takahashi, *J. Chem. Soc., Perkin Trans. 1*, in press.
8. Data for **2a**: pale yellow oil; ν_{max}(neat)/cm^{-1} 1747 (C=O), 1248 (C-O) and 1185 (C-O); ^{1}H-NMR(400 MHz, $CDCl_3$) δ 0.88 (3 H, t, J=7.0, CH_3), 1.29-1.36 (2 H, m, CH_2), 1.41-1.48 (2 H, m, CH_2), 1.76-1.86 (2 H, m, CH_2), 1.93-1.99 (2 H, m, CH_2), 3.61 (1 H, t, J=7.0, CH), 5.25 (1 H, d, J=14.1, CH_2), 5.46 (1 H, d, J=14.1, CH_2), 7.18-7.22 (2 H, m, Ph), 7.29-7.37 (2 H, m, Ph); ^{13}C-NMR(100 MHz, $CDCl_3$) δ 13.9, 22.3, 26.7, 30.4, 31.4, 46.0, 69.4, 124.6, 126.7, 127.1, 128.5, 130.9, 134.9, 172.9; m/z (EI) 218 (M^+); (Found: C, 77.2; H, 8.6; $C_{14}H_{18}O_2$ requires C, 77.0; H, 8.3%).
9. The structure of indanone **3a** has been identified by spectral analysis:



3a

10. The molecular structure of **5i** has been established by an X-ray crystallographic analysis. Data for **5i**: collorless needles; ν_{max}(neat)/cm^{-1} 1732 (C=O), 1626 (C=C) and 1230 (C-O); ^{1}H-NMR(400 MHz, $CDCl_3$) δ 2.06 (6H, s, 2 × CH_3), 2.30 (3H, s, CH_3), 5.31 (2H, s, CH_2), 6.79 (1H, d, J=7.8, Ph), 6.86 (2H, s, Ph), 7.00-7.04 (1H, t, J=6.3, Ph), 7.19-7.24 (2H, m, Ph); ^{13}C-NMR(100 MHz, $CDCl_3$) δ 19.9, 21.0, 69.1, 124.5, 125.9, 126.7, 128.1, 128.3, 128.7, 131.1, 131.2, 131.3, 135.7, 137.8, 139.1, 167.9; m/z (EI) 280 (M^+); (Found: C, 81.7; H, 6.4; $C_{19}H_{18}O_2$ requires C, 81.9; H, 6.5%)
11. S. Takahashi, Y. Kuroyama, K. Sonogashira, and N. Hagihara, *Synthesis*, **1980**, 627.